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(54) Title: COMPOUND LIBRARIES

(57) Abstract: The present invention relates to compounds capable of binding to the active site of protein kinase enzymes. The invention further relates to libraries of compounds and a family of libraries of compounds for use in screening programmes against protein kinases as well as the individual compounds for use in hit to lead and lead optimisation projects, and similar stages in the drug discovery process. The invention also provides methods for making compounds and libraries.

COMPOUND LIBRARIES

The present invention relates to compounds capable of binding to the active site of protein kinase enzymes. In particular, a family of libraries of compounds is provided for use in screening programmes against protein kinases as well as the individual compounds for use in hit to lead and lead optimisation projects, and similar stages in the drug discovery process. The invention also provides methods for making compounds and libraries.

As part of the process of discovering drugs or agrochemicals it is customary to screen libraries of compounds against biological targets to discover 'hits' which are then further developed into 'leads' and subsequently drugs or agrochemicals, by using the techniques of medicinal chemistry. Accordingly the success or not of the drug or agrochemical discovery project is critically dependant on the quality of the hit and this in turn is dictated by the quality of the screening library.

Technological advances have enabled screening on a very large scale, and the screening of hundreds and thousands of compounds at the start of a discovery program is routine. This does, however, entail a significant cost. The hits obtained from such screening efforts are not all of the best quality, and often take a large amount of subsequent time and effort in order to get a good lead. It has been estimated that only about 25% of projects actually get to the lead optimisation stage, and part of the reason for this is the intractability of hits from high throughput screening.

Screening libraries are commonly collections of compounds from several sources. As a result they typically contain compounds synthesised as part of previous projects in the history of a company. With regard to drug discovery, these collections will be drug-like but are likely to be limited in scope and will be directed to certain areas of a project. It has been the common practice of many pharmaceutical companies in recent times to augment the collections by purchasing either single compounds from

vendors, or by contracting the synthesis of combinatorial libraries of compounds. The singly purchased compounds may have been selected to fill in areas of compound space poorly represented in the compound collections. Combinatorial libraries are typically synthesised around well-performing chemistries with some design based on producing 'diversity' in compound space.

A complementary approach, and one that is increasingly preferred, is to screen focused libraries against the target of choice. Focused libraries are becoming of increasing importance in their ability to generate hits capable of rapid expansion in many areas including kinases. Such libraries are slightly more expensive to prepare but have attributes of reliability, reproducibility and provide a considerably higher hit rate: typically 10-100 fold and above compared with random screening. They are, however, very difficult to design and their efficiency relates directly to the amount of effort that has gone into the design. Using these focused libraries it is usually possible to get a number of hits in the low micromolar and below range. As there is a defined set of compounds, the potential exists to observe indications of SAR in a chemical series, and to progress the chemistry efficiently.

Protein kinases constitute approximately 2% of the human genome and are fundamental to many intracellular signalling processes. They form the largest known family of enzymes and act on specific proteins within cells. Through the phosphorylation of specific sites, protein kinases are responsible for the activation or deactivation of various signaling transduction pathways. Abnormalities in the phosphorylation mechanism are a major factor in many disease states including cancer, diabetes and inflammation.

In a bid to control these disease states, protein kinases have been the focus of attention and the subject of much research for many years. However, since the development of the first inhibitors back in the early

1980's, there remains a shortage of clinically approved protein kinase inhibitors, with only a limited number of therapeutic agents currently in use. The discovery of safe and selective kinase inhibitors therefore remains highly desirable and is still widely sought after.

The family of focused libraries provided herein is designed to interact with a range of kinase targets. Each library is a defined set of compounds which will enhance the probability of finding a small molecule which will interact with one or more types of protein kinases. Protein crystallography has allowed for the preparation of three-dimensional structures detailing the individual protein sequence alignments of the catalytic domains of many different protein kinases. These can be used to not only identify commonalities in the general structure of protein kinases, but also to ascertain sequences which are unique to the individual kinases.

Advantagously, the invention provides a family of 'focused' libraries of compounds which will provide clear leads for ligands which bind to the active site of protein kinase enzymes. Remarkably, focused libraries according to this invention can provide hit rates of typically 1-13% for the requisite predicted protein kinases. The libraries are defined in detail below and are referred to herein as SFK09, SFK10, SFK11, SFK14 and SFK20 wherein SFK represents "soft focus kinase library" and the suffixed numbers identify individual libraries.

In the context of the present invention, 'library' means a group of compounds which are structurally related by virtue of a core chemical structure (or 'scaffold'), but which differ from each other by virtue of permutation of specific substituent groups attached to the scaffold. The core chemical structures are referred to as, for example, PS40, PS81 and PS172 (the scaffolds of SFK09 having general formulae I, II and III respectively) wherein PS represents "pharmascape" and the suffixed numbers identify individual scaffolds.

Generally speaking such a library will consist of or comprise a number of compounds, e.g. as many as about 100, about 1000, about 2000, about 3000 or indeed about 10000 compounds. The word 'about' is interpreted to mean plus or minus 20%, more preferably plus or minus 10%, most preferably plus or minus 5% The number of compounds should be sufficient to provide an adequate diversity of related compounds without being so large to be unduly complex or expensive to produce.

The word 'comprises' is interpreted to mean 'includes among other things' and is not interpreted to mean 'consists of only'.

In the context of the present invention the term 'a set of' is interpreted to mean 'a plurality of'.

In the context of the present invention the terms 'permitted substituents' and analogous terms are used to refer to defined chemical groups that may be attached to a 'scaffold' to provide permutations of the chemical structure of related compounds.

Where the chemical formulae of permitted substituents are shown in this description and claims, the substituent may appear in the compounds as shown (i.e. simply covalently bonded to the scaffold) or may be a derivative of the shown chemical formula of the substituent by virtue of the use of a reactive group to couple the substituent to the scaffold. Polymerisation of permitted substituents (e.g. diamerisation) is intended to be within the scope of the invention.

It will be appreciated that the total number of permutations created by the permitted substituents may be a very large number, far greater in magnitude than the actual number of compounds in the library. In other words, the number of possible compounds for any 'virtual' library may well greatly exceed the number of synthesised compounds making up an embodiment of the 'real' library. The invention is intended to encompass

libraries having all, and a number which is less than all, of the permitted substitutions represented by compounds therein.

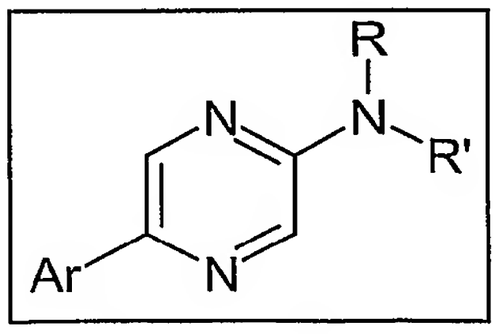
It will be appreciated that some specific combinations of permitted substituents may be more or less difficult to synthesise and/or use in a focused library of the invention. This does not detract from the generality of applicability of the invention as described herein. Real libraries have been synthesised from a selected group of permutations/combinations of permitted substituents, taking into consideration factors affecting the intended purpose of the library and its cost and complexity of synthesis.

In a first aspect the invention provides a library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II and/or formula III of library SFK09.

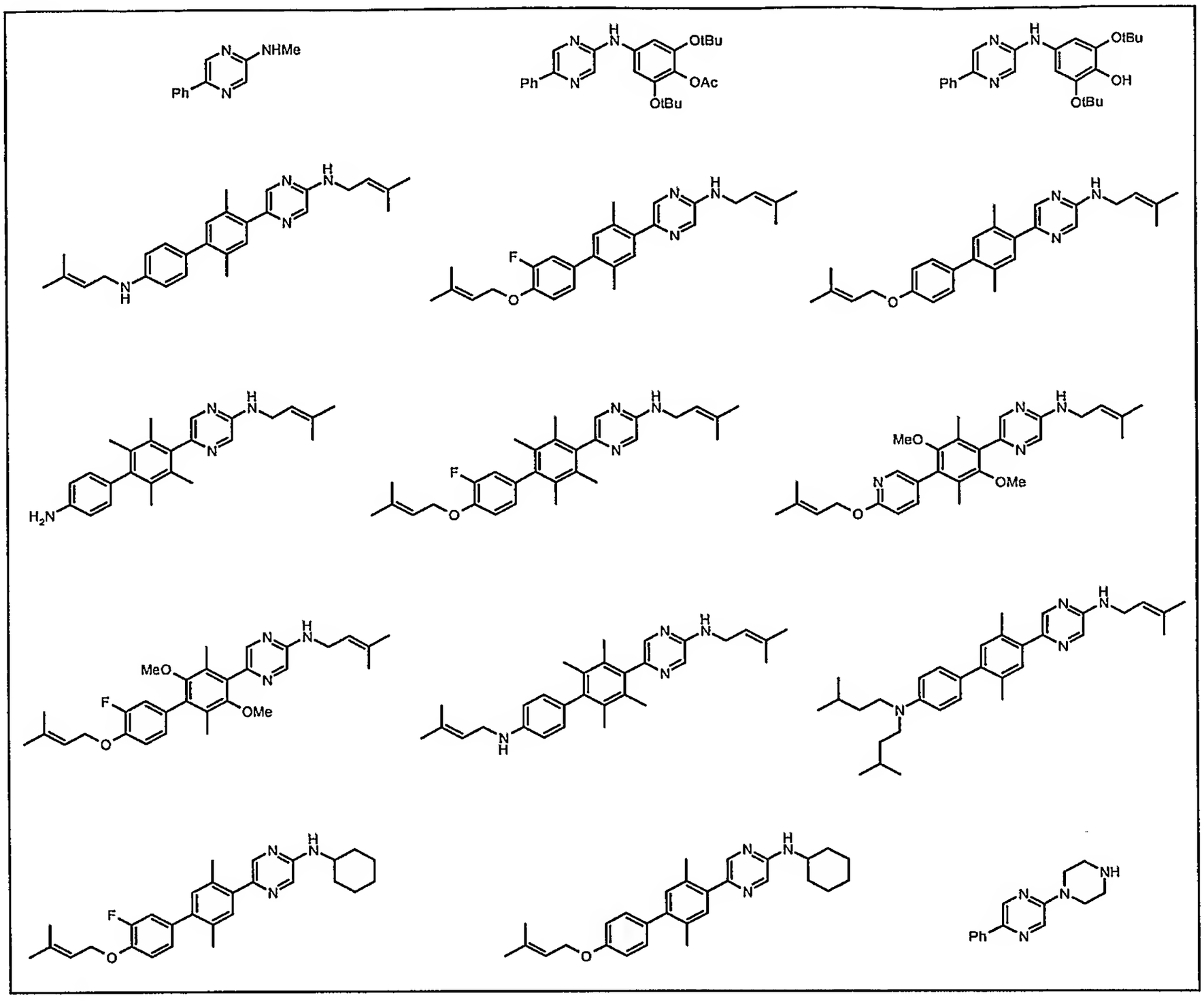
Preferably an embodiment of the library comprises or consists of a structurally related set of compounds, said library being library SFK09.

In a second aspect the invention provides a compound having a core chemical structure (scaffold) of SFK09 which is selected from:

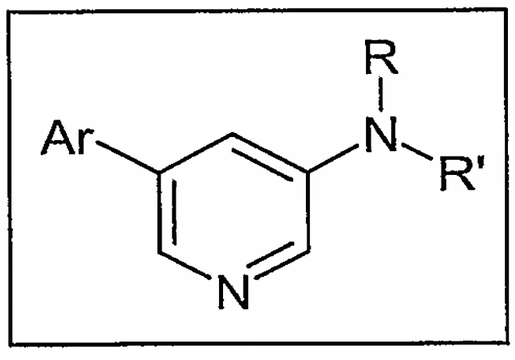
i) PS40



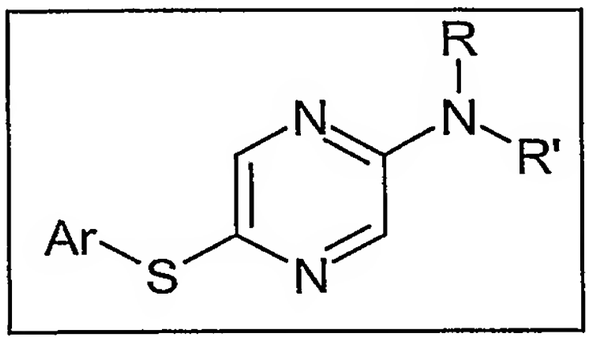
excluding the following compounds



ii) PS81


;or

iii) PS172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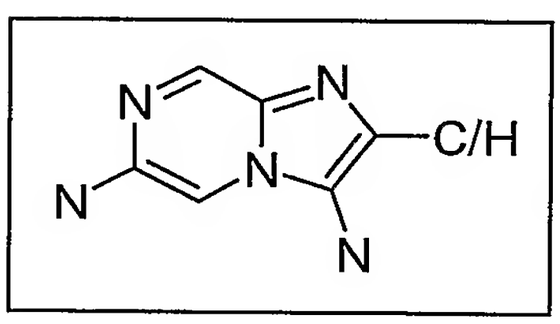
Preferably an embodiment of a compound according to this aspect of the invention is selected from the compounds represented within the library SFK09.

In a third aspect the invention provides a library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II and/or formula III of library SFK10.

Preferably an embodiment of the library comprises or consists of a structurally related set of compounds, said library being library SFK10.

In a fourth aspect the invention provides a compound having a core chemical structure (scaffold) of SFK10 which is:



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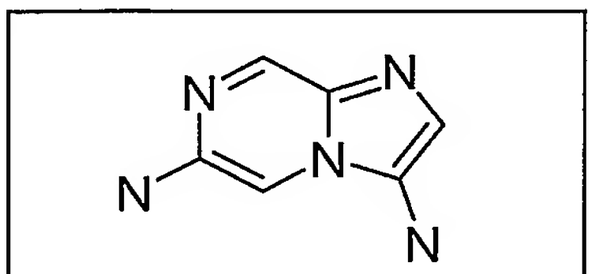
Preferably an embodiment of a compound according to this aspect of the invention is selected from the compounds represented within the library SFK10.

In a fifth aspect the invention provides a library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II and/or formula III of library SFK11.

Preferably an embodiment of the library comprises or consists of a structurally related set of compounds, said library being library SFK11.

In an sixth aspect the invention provides a compound having a core chemical structure (scaffold) of SFK11 which is:



SFK11 Core Scaffold

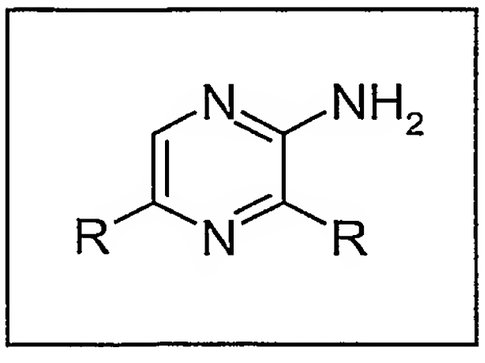
Preferably an embodiment of a compound according to this aspect of the invention is selected from the compounds represented within the library SFK11.

In a seventh aspect the invention provides a library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II of library SFK14.

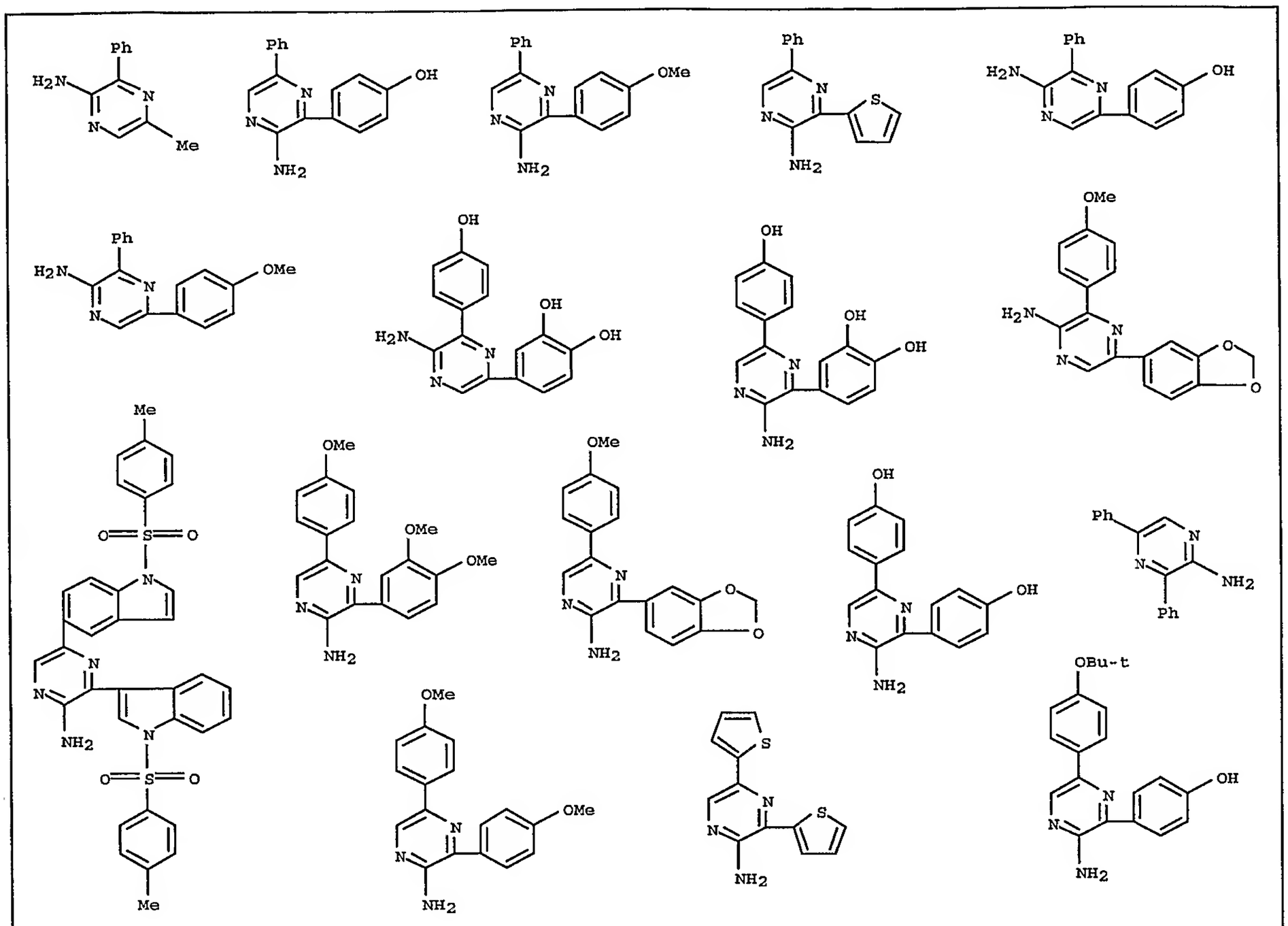
Preferably an embodiment of the library comprises or consists of a structurally related set of compounds, said library being library SFK14.

In an eighth aspect the invention provides a compound having a core chemical structure (scaffold) of SFK14 which is selected from:

i) PS173

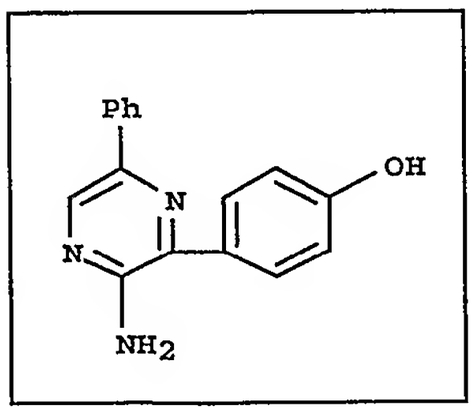


excluding:



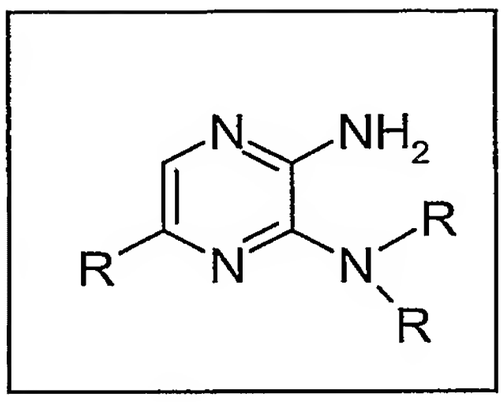
Mentioned in literature

and



; or

ii) PS174

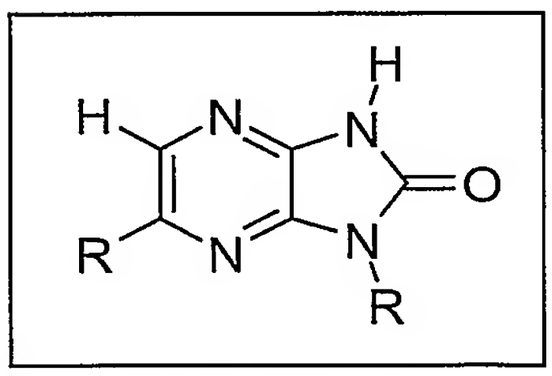


Preferably an embodiment of a compound according to this aspect of the invention is selected from the compounds represented within the library SFK14.

In a ninth aspect the invention provides a library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I of library SFK20.

Preferably an embodiment of the library comprises or consists of a structurally related set of compounds, said library being library SFK20.

In a tenth aspect the invention provides a compound having a core chemical structure (scaffold) of SFK20 which is:



Preferably an embodiment of a compound according to this aspect of the invention is selected from the compounds represented within the library SFK20.

Preferably, an embodiment of a library according to the invention comprises compounds having a core chemical structure and permitted

substituents thereon, and said library has all or substantially all of the permitted substitutions represented by compounds therein.

Preferably, an embodiment of a library according to the invention comprises compounds having a core chemical structure and permitted substituents thereon, and said library has about 100, about 1000, about 2000, about 3000 or about 10000 compounds represented therein.

In an eleventh aspect the invention provides a method for making a compound library according to an aspect of the invention, which method is according to any of the schemes for making a core chemical structure (scaffold) of a library selected from:

i) library SFK09;

ii) library SFK10;

iii) library SFK11;

iv) library SFK14; and

v) library SFK20.

Most of the compounds defined by the permitted substitutions on the scaffolds are also novel per se and the invention is intended to encompass each individual novel compound. Any known compound having a structural formula identical to any one of the compounds covered by the formulae of scaffolds and permitted substitutions described herein is hereby explicitly disclaimed per se.

In a further aspect the invention provides a method of making a compound according to an embodiment of the invention which method is according to any of the schemes defined herein for making compounds of a library selected from the group of libraries which consists of:

i) library SFK09;

ii) library SFK10;

iii) library SFK11;

iv) library SFK14; and

v) library SFK20.

In a further aspect the invention provides an assay comprising a family of libraries, a library, or one or more compounds according to the invention.

In a further aspect the invention provides use of an assay according to an embodiment of the invention for identifying a compound which has therapeutic affect.

In a further aspect the invention provides a pharmaceutical composition which comprises a compound according to the invention or a compound identified in an assay according to an embodiment of the invention.

In a further aspect the invention provides a compound having a core chemical structure (scaffold) of a library selected from the group of libraries which consists of:

i) library SFK09;

ii) library SFK10;

iii) library SFK11;

iv) library SFK14; and

v) library SFK20

or a compound according to an embodiment of the invention for use in therapy.

In a further aspect the invention provides use of a compound having a core chemical structure (scaffold) of a library selected from the group of libraries which consists of:

i) library SFK09;

ii) library SFK10;

iii) library SFK11;

iv) library SFK14; and

v) library SFK20

or a compound according to an embodiment of the invention in the manufacture of a medicament for treatment or prophylaxis of a condition characterised by abnormal kinase activity.

In a further aspect the invention provides use of a compound having a core chemical structure (scaffold) of a library selected from the group of libraries which consists of:

i) library SFK09;
ii) library SFK10;
iii) library SFK11;
iv) library SFK14; and
v) library SFK20

or a compound according to an embodiment of the invention in the manufacture of a medicament for treatment or prophylaxis of a condition selected from cancer, a tumour, metastases, inflammation or diabetes.

In a further aspect the invention provides a family of libraries of compounds for high throughput investigation of a predetermined kinase enzyme wherein the family includes the libraries SFK09, SFK10, SFK11, SFK14 and SFK20. In use, the family of libraries is checked for the library or libraries most likely to include a hit which interacts with the predetermined kinase and these libraries are used for high throughput investigation.

In a further aspect the invention provides a method for making a family of libraries according to the invention, which method is according to the schemes defined herein.

The invention will now be described in detail with reference to specific examples of compounds and methods for their production. The libraries SFK09, SFK10, SFK11, SFK14 and SFK20 and compounds within these libraries will be described in turn.

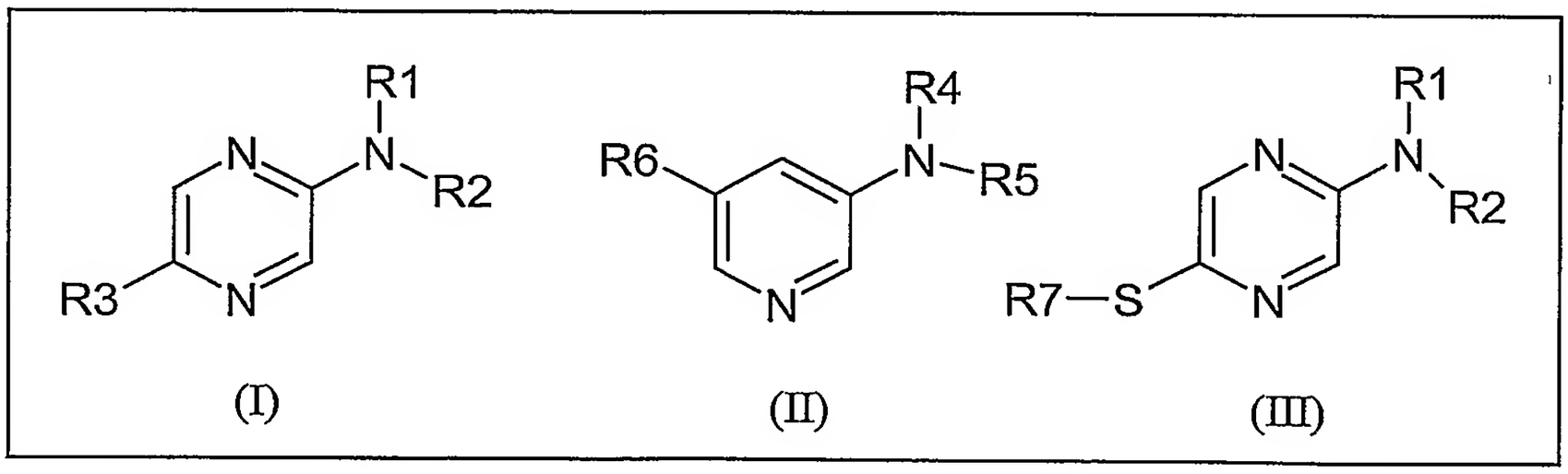
Within this specification embodiments have been described in a way which enables a clear and concise specification to be written, but it will be appreciated that embodiments may be variously combined or separated without parting from the invention.

LIBRARY SFK09

SFK09 is designed to have a broad focus on the tyrosine and serine/threonine kinases that recognise typical mono-and bicyclic heterocyclic ligands for the ATP binding site. The central design of the library is based on novel applications of the 3-amino-5-carba-pyridine, 2-amino-5-carba-pyrazine and 2-amino-5-thia-pyrazine scaffolds.

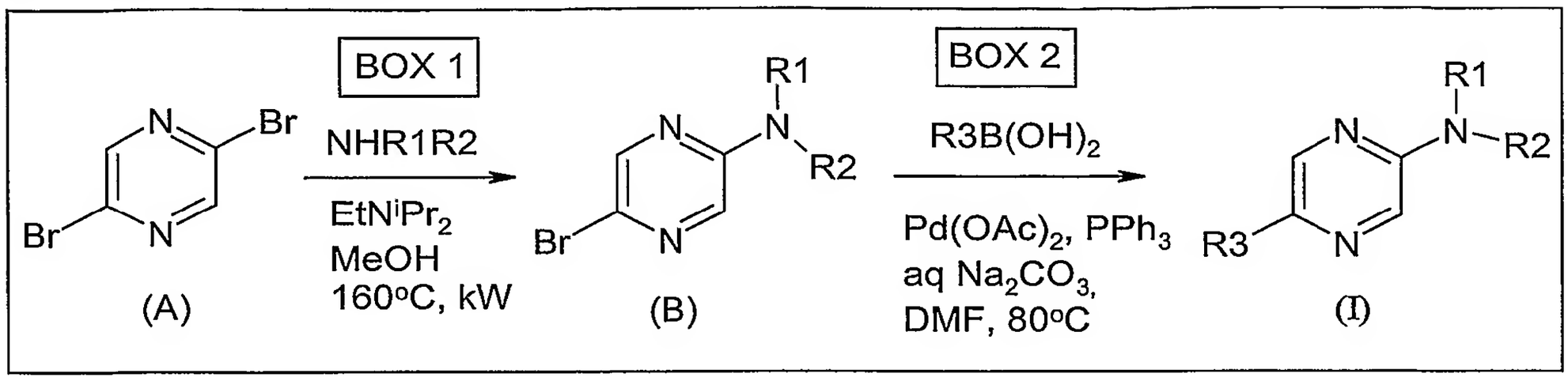
Each scaffold was docked into the ATP-binding region of a variety of kinases including Zap-70, CDK-2, CDK-4, p38 MAP kinase and FGF-r. PS40 exhibits the characteristic double H-bonding system seen between ATP and the enzyme backbone in all the ATP sites examined and particularly favourable docking modes were observed for the tyrosine kinases. PS81 exhibits a single H-bond between Ala^{417} of Zap-70 and the pyridine ring-N can form an additional H-bond to the backbone distinct from the more usual "amidine" H-bond, especially in the tyrosine kinases that were examined.

The invention provides a compound library comprising or consisting of a set of structurally related compounds of the general formula (I), (II) and (III):

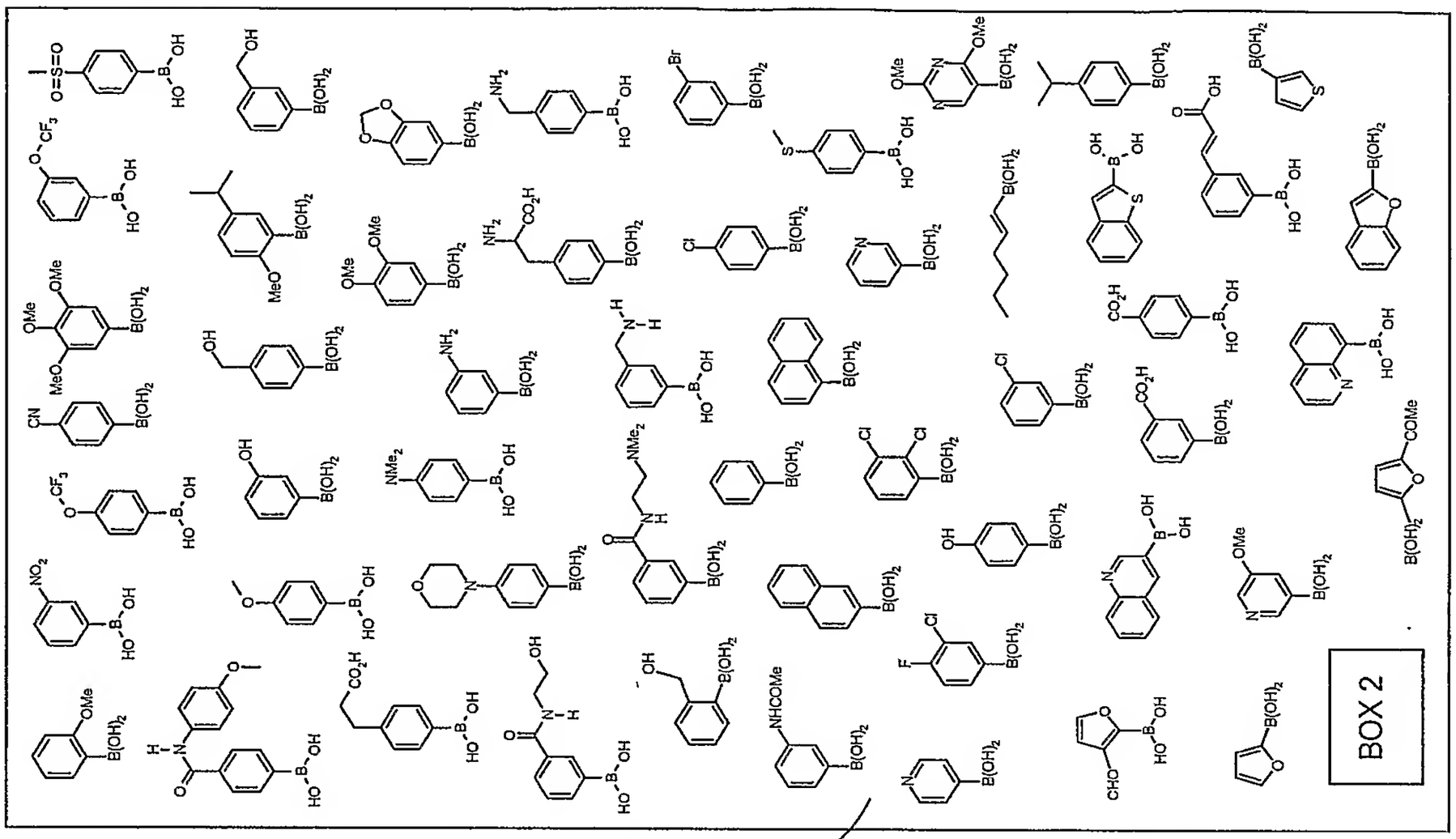


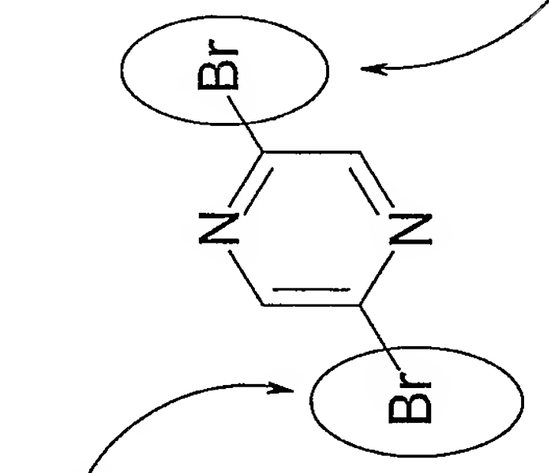
Wherein R1, and R4 is hydrogen; R2 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; R3 and R6 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; R5 is aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; R7 is aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position. R1 and R2 may also be joined to form the same ring system.

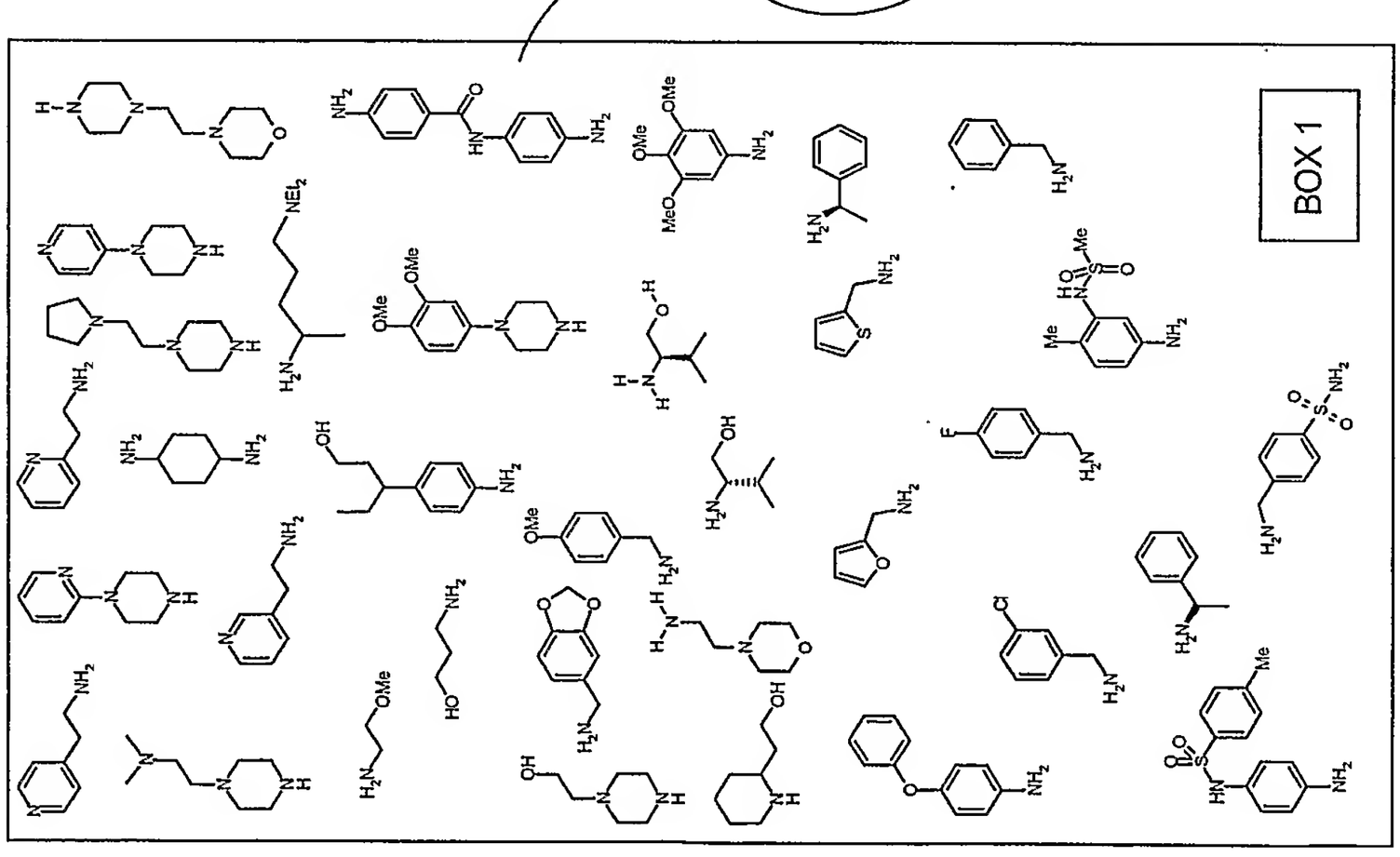
Scheme for synthesising compounds of formula (I) (PS40)



2,5-Dibromopyrazine (A) can be aminated with the amines described in Box 1. The resultant compounds (B) can then be reacted with the boronic acids described in Box 2 to yield the final compounds with formula (I).

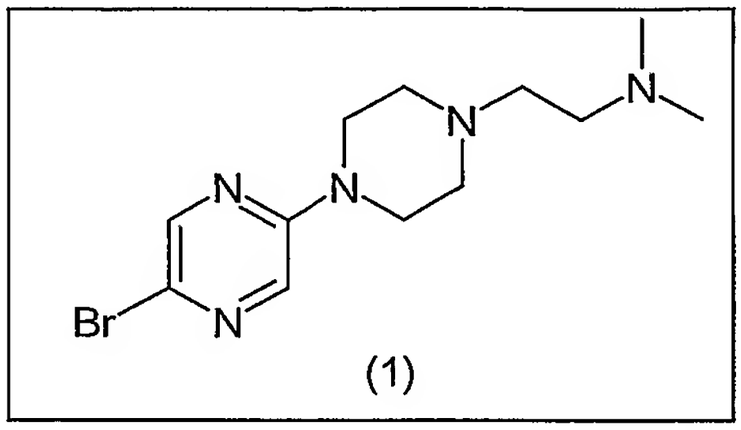

BOX 2




BOX 1

General Procedures:

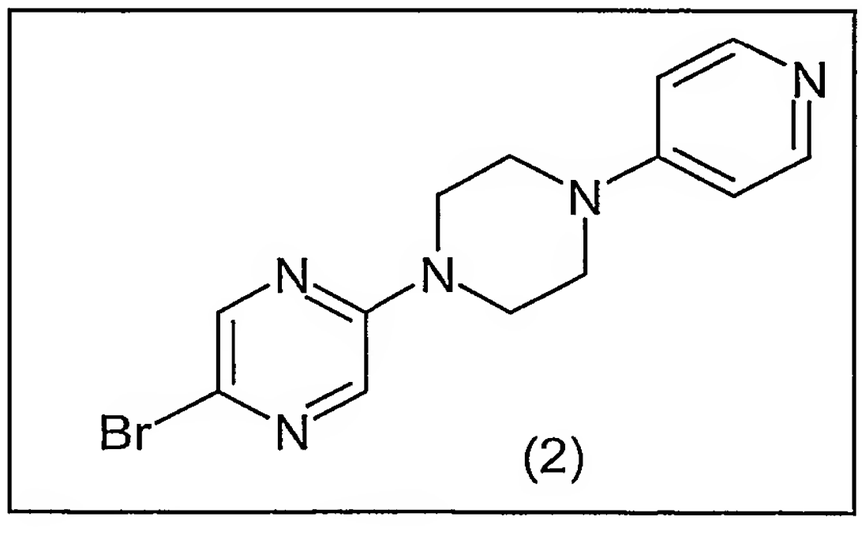
Typical example of compound of formula (B), as described in the general reaction scheme; *[2-(5'-bromo-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-ethyl]-dimethyl-amine* ***(1)***.



(1)

Dimethylaminoethylpiperazine (5mmol), 2,5-dibromopyrazine (5mmol) and Hunig's base (5mmol) in methanol (2ml) was heated to 160°C for 10 min. The reaction was taken up in DCM. The solution was washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant solid was washed with hexane/DCM (9/1) to afford the desired product (1.07g, 65%). ^1H (270MHz, $CDCl_3$) 2.42(6H, s, $N(CH_3)_2$), 2.58-2.63(8H, m, $4xCH_2$), 3.56-3.60(4H, t, *J* 5Hz, $2xCH_3$), 7.85(1H, s, Ar), 8.12(1H, s, Ar); HPLC: R_t 1.09 (98.70%); *m/z* (ES): 314 (100%, M+H), 271 (95%, M-$N(CH_3)_2$).

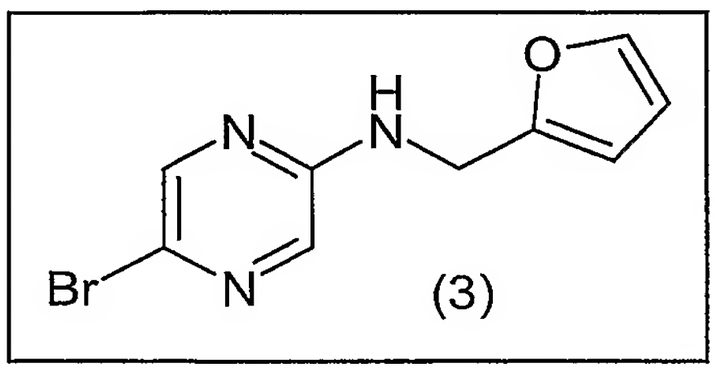
Typical example of compound of formula (B), as described in the general reaction scheme; *5'-bromo-4-pyridin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl* ***(2)***.



(2)

Yield 3.3g, 33%; $^{\delta}$H (270MHz, $CDCl_3$) 3.49-3.54 (2H, m), 3.73-3.77 (2H, m), 6.69-6.72 (2H, m), 7.91-7.92 (1H, d, *J* 1.4), 8.17-8.18 (1H, d, *J* 1.4); HPLC 87%; *m/z* (ES) 321 $[M+H]^+$.

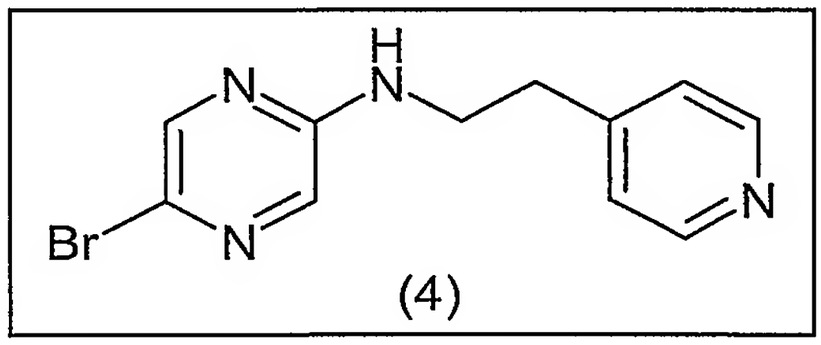
Typical example of compound of formula (B), as described in the general reaction scheme; *(5-bromo-pyrazin-2-yl)-furan-2-ylmethyl-amine* ***(3)***.



(3)

Yield 7.35g, 99%; $^{\delta}$H (270MHz, $CDCl_3$) 4.52-4.54 (2H, d, *J* 5.6), 4.91-4.95 (1H, br.s), 6.25-6.27 (1H, m), 6.32-6.34 (1H, m), 7.36-7.38 (1H, m), 7.72-7.73 (1H, d, *J* 1.4), 8.11-8.12 (1H, d, *J* 1.4); HPLC 99%; *m/z* (ES) 256 $[M+H]^+$.

Typical example of compound of formula (B), as described in the general reaction scheme; *(5-Bromo-pyrazin-2-yl)-(2-pyridin-4-yl-ethyl)-amine* ***(4)***.



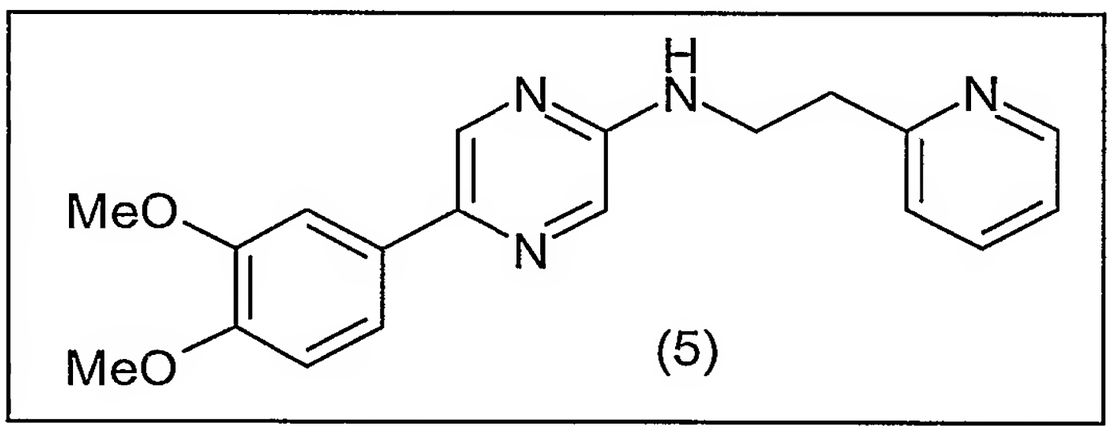
(4)

Yield 6.4g, 93%; $^{\delta}$H (270MHz, $CDCl_3$) 2.91-2.96 (2H, t, *J* 6.8), 3.62-3.70 (2H, m), 7.14-7.16 (2H, m), 7.64-7.65 (1H, d, *J* 1.2), 8.10-8.11 (1H, d, *J* 1.2), 8.52-8.55 (2H, m); HPLC 82%; *m/z* (ES) 279 $[M+H]^+$.

General procedure for the synthesis of compounds of formula (I).

The Suzuki reactions were carried out in stem tubes using a 96 position STEM shaker. To a solution of the required intermediates (B) in DMF (0.3mmol, 0.5ml) was added a solution of boronic acid (Box 2) in DMF (0.36mmol, 0.6ml) and 1.5M Na_2CO_3(aq.) solution (0.75mmol, 0.5ml). The reaction vessels were then placed in a nitrogen filled glovebox for 30min. Two solutions of palladium acetate (95mg) and triphenylphosphine (335mg) in 1,4-dioxane (15ml) were freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml) was added to each reaction vessel inside the glovebox. The vessels were screw capped and then heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative reverse phase HPLC.

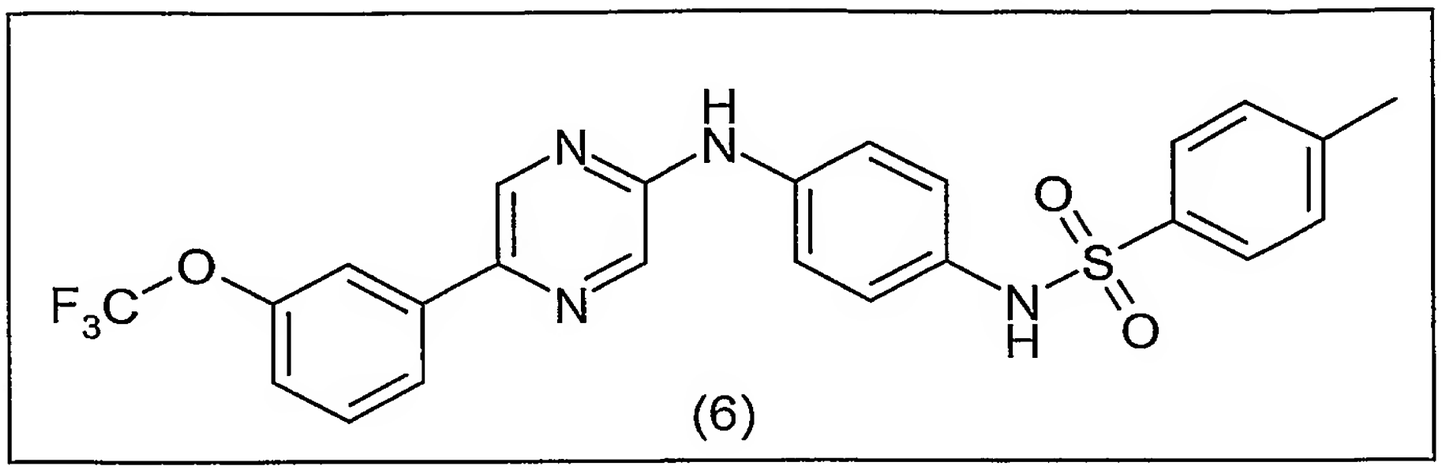
Typical example of compound of formula (I), as described in the general reaction scheme; *[5-(3,4-dimethoxy-phenyl)-pyrazin-2-yl]-(2-pyridin-2-yl-ethyl)-amine* ***(5)***.



(5)

Yield 51.9mg, 51%; $^{\delta}H$ (250MHz, $CDCl_3$) 1.25(1H, br.s), 3.45-3.50 (2H, m), 3.92-4.02 (8H, m) 6.90-6.93 (1H, m), 7.29-7.33 (1H, m), 7.43-7.44 (1H, m), 7.60-7.66 (1H, m), 7.77-7.80 (1H, m), 8.15-8.22 (2H, m), 8.6-8.69 (1H, m); HPLC 100%; *m/z* (ES) 337 $[M+H]^+$.

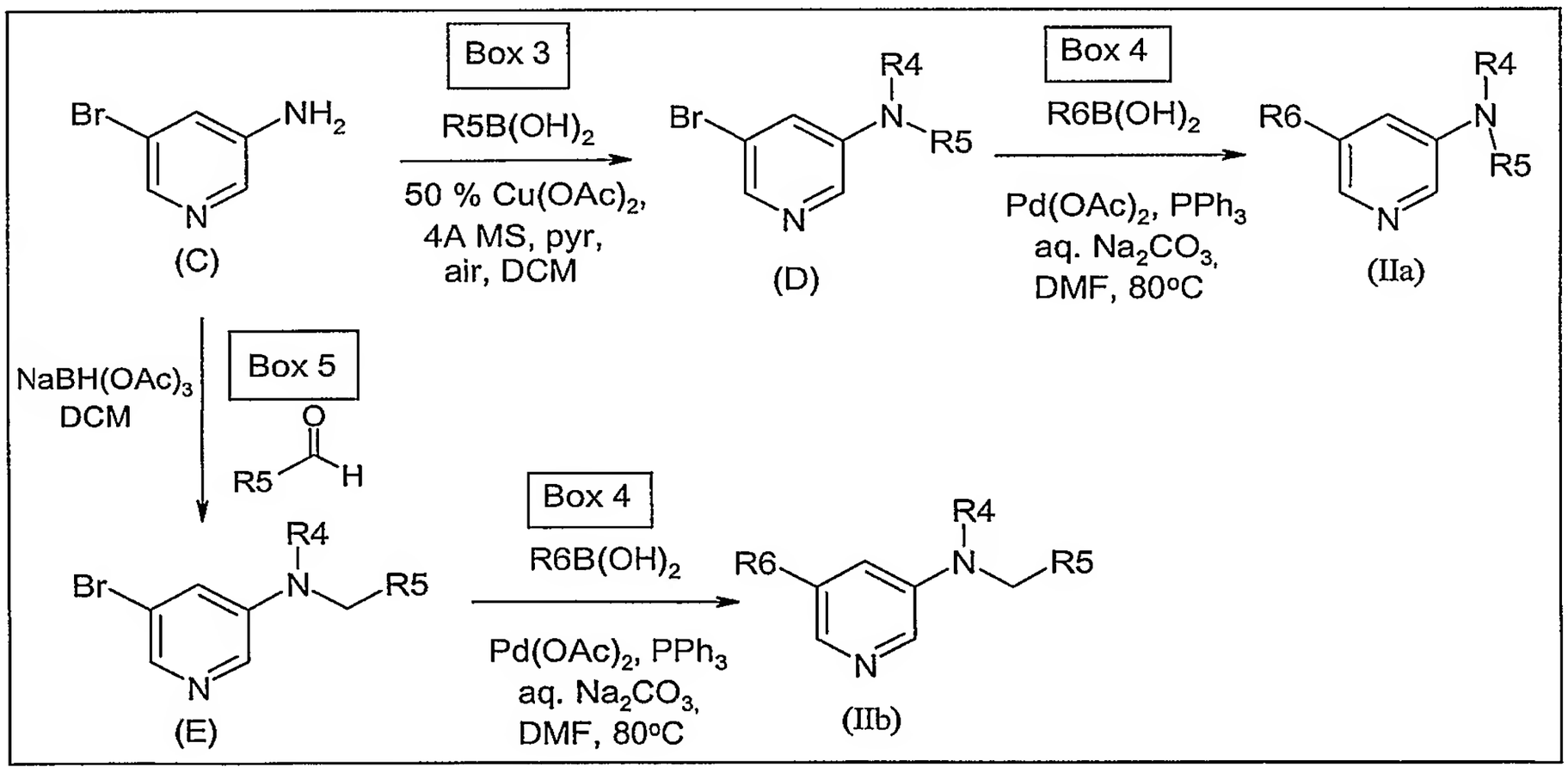
Typical example of compound of formula (I), as described in the general reaction scheme; *4-methyl-N-{4-[5-(3-trifluoromethoxy-phenyl)-pyrazin-2-ylamino]-phenyl}-benzenesulfonamide* ***(6)***.



(6)

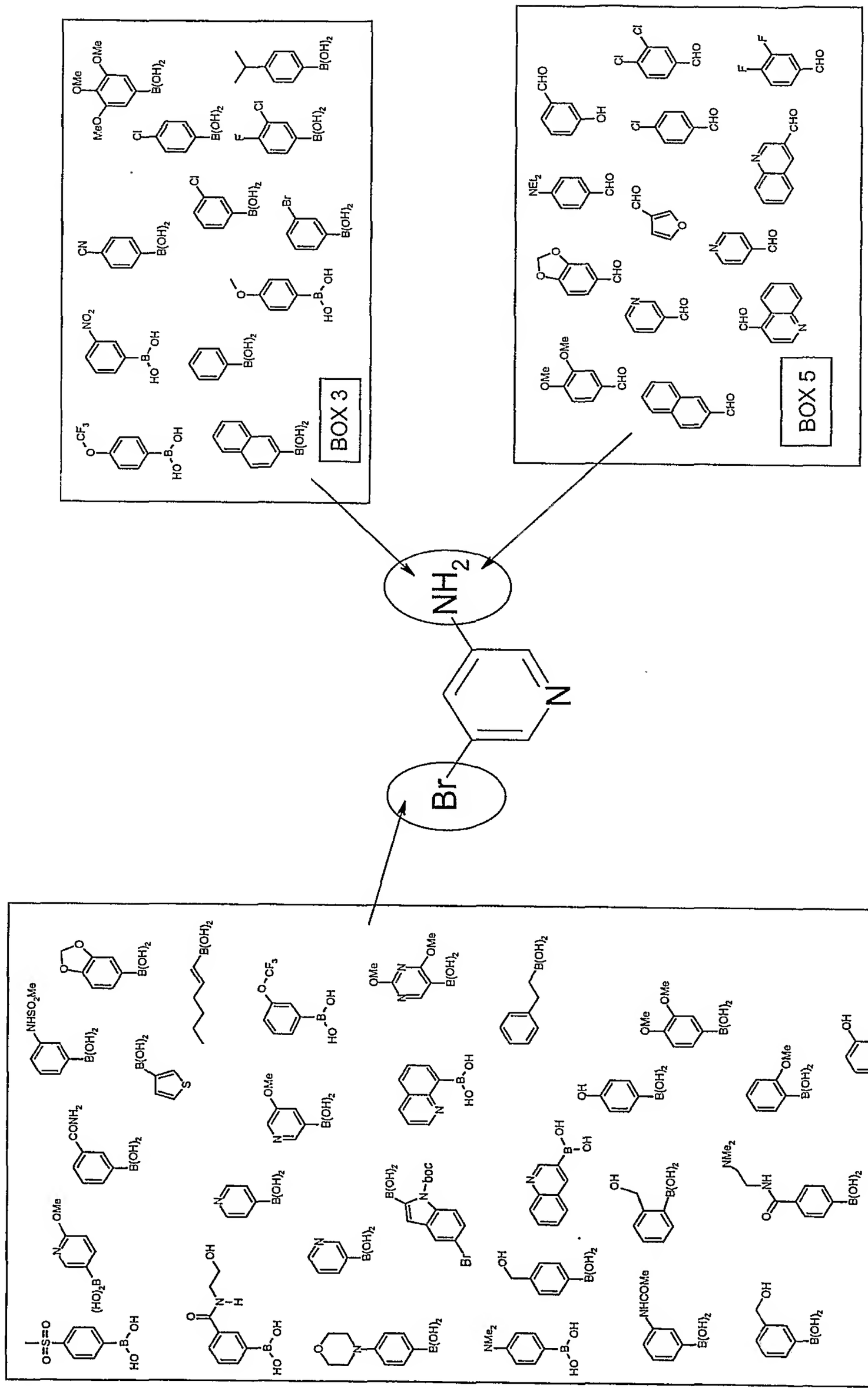
Yield 73.5mg, 50%; $^{\delta}$H (250MHz, $CDCl_3$) 2.39(3H, s) 6.82-6.89 (2H, m), 7.06-7.09 (2H, m) 7.10-7.25 (1H, m), 7.38-7.51 (3H, m), 7.63-7.66 (2H, m), 7.79-7.83 (2H, m), 8.23-8.24 (1H,d, *J* 1.4), 8.54-8.55 (1H, d, *J* 1.4); HPLC 100%; *m/z* (ES) 501 $[M+H]^+$.

Scheme for synthesising compounds of formula (II) - (IIa and IIb - PS81)



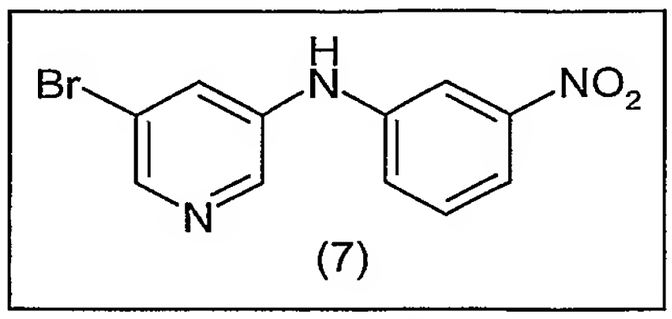
3-Amino-5-bromopyridine (C) can be subjected to a copper mediated N-arylation with the boronic acids described in Box 3, and the resultant compounds (D) then reacted with the boronic acids described in Box 4 to yield final compounds of formula (IIa). Alternatively, compounds with the general structure (E) can be synthesised through a reductive amination with the aldehydes described in Box 5. Functionalisation at C5 with the

boronic acids described in Box 4 yields final compounds with the general formula (IIb).


BOX 3
BOX 5
BOX 4
NH2
Br
N

General Procedures:

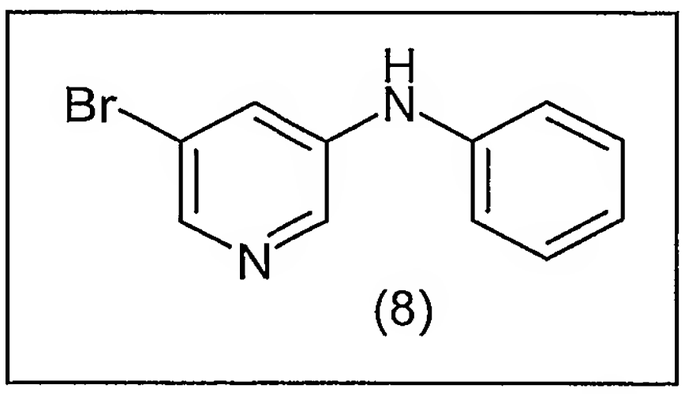
Typical example of compound of formula (D), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-(3-nitro-phenyl)-amine* ***(7)***.



(7)

3-Amino-5-bromopyridine (3.11g, 18mmol), 3-nitrophenylboronic acid (6.28g, 36mmol), copper(II) acetate (1.63g, 9mmol), 4Å molecular sieves (3g) and pyridine (2.9 ml, 36mmol) in DCM (50ml) was stirred vigorously in an open top vessel for 18h. The reaction was filtered and the residue was washed with methanol. SiO_2 (10g) was added to the solution and concentrated *in vacuo* to dryness. The resultant solid was chromatographed (SiO_2, 20%-50% EtOAc in hexane) to afford the desired product (1.61g, 30%) as a bright yellow solid. ^1H (270MHz, $CDCl_3$) 6.08(1H, br.s, NH), 7.39-7.40(1H, m, r), 7.45-7.60(1H, m, Ar), 7.62(1H, s, Ar), 7.83-7.89(2H, m, Ar), 8.34-8.37 (2H, m, Ar); HPLC: R_t 2.06 (77.89%); *m/z* (ES): 294(100%, M^+).

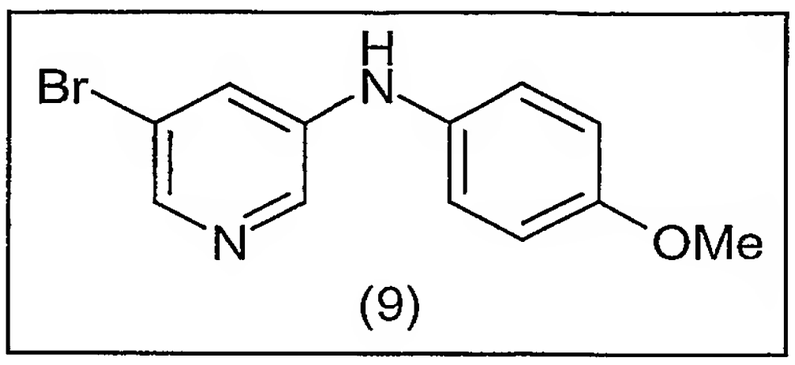
Typical example of compound of formula (D), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-phenyl-amine* ***(8)***.



(8)

Yield 860mg, 35%; $^{\delta}H$ (250MHz, $CDCl_3$) 5.87 (1H, br.s), 7.07-7.53 (6H, m), 8.16-8.24 (2H, m); HPLC 92%; *m/z* (ES) 249 $[M+H]^+$.

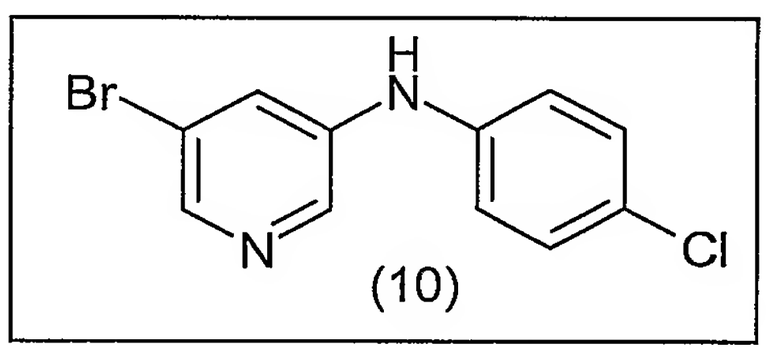
Typical example of compound of formula (D), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-(4-methoxy-phenyl)-amine* ***(9)***.



(9)

Yield 1.27g, 38%; $^{\delta}$H (250MHz, $CDCl_3$) 3.82 (3H, s) 5.61 (1H, br.s), 6.89-6.92 (2H, d, J 8.9) 7.07-7.11 (2H, d, J 8.9), 7.27-7.29 (1H, m) 8.06-8.11 (2H, m); HPLC 100%; *m/z* (ES) 279 $[M+H]^+$.

Typical example of compound of formula (D), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-(4-chloro-phenyl)-amine* ***(10)***.



(10)

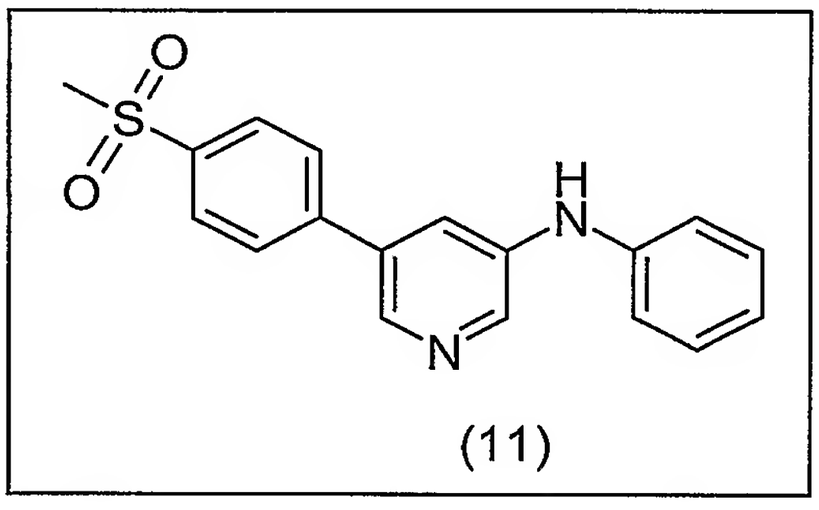
Yield 760mg, 30%; $^{\delta}$H (250MHz, $CDCl_3$) 6.11 (1H, br.s), 7.02-7.06 (2H, d, J 8.8) 7.27-7.31 (2H, d, J 8.8), 7.48-7.50 (1H, m) 8.18-8.24 (2H, m); HPLC 90%; *m/z* (ES) 283 $[M+H]^+$.

<u>General procedure for the synthesis of compounds of formula (IIa).</u>

The Suzuki reactions were carried out in stem tubes using a 96 position STEM shaker. To a solution of the required intermediates (D) in DMF (0.3mmol, 0.5ml) was added a solution of boronic acid (Box 4) in DMF (0.36mmol, 0.6ml) and 1.5M Na_2CO_3(aq.) solution (0.75mmol, 0.5ml). The reaction vessels were then placed in a nitrogen filled glovebox for

30min. Two solutions of palladium acetate (95mg) and triphenylphosphine (335mg) in 1,4-dioxane (15ml) were freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml) was added to each reaction vessel inside the glovebox. The vessels were screw capped and then heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative reverse phase HPLC.

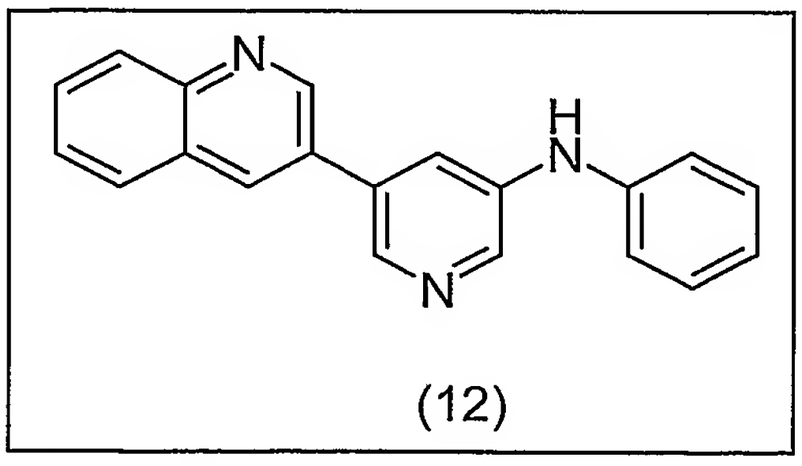
Typical example of compound of formula (IIa), as described in the general reaction scheme; *[5-(4-methanesulphoylphenyl)pyridin-3-yl]-phenylamine* **(11)**.



(11)

Yield 17mg, 17%; $^{\delta}H$ (250MHz, $CDCl_3$) 3.86 (3H, s), 6.23-6.43 (6H, m) 7.63-7.71 (3H, m), 7.95-7.96 (2H, m), 8.33-8.34 (2H, m); HPLC 100%; *m/z* (ES) 325 $[M+H]^+$.

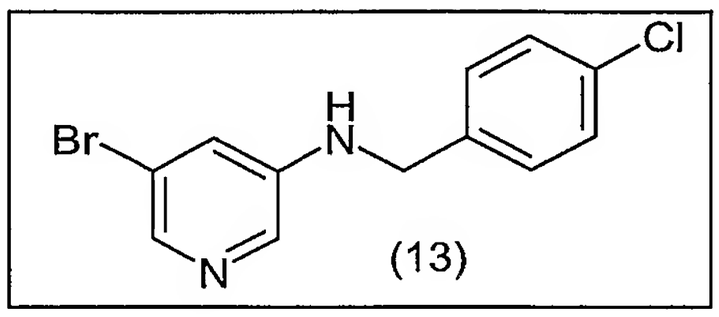
Typical example of compound of formula (IIa), as described in the general reaction scheme; *phenyl-(5-quinolin-3-yl-pyridin-3-yl)amine* **(12)**.



(12)

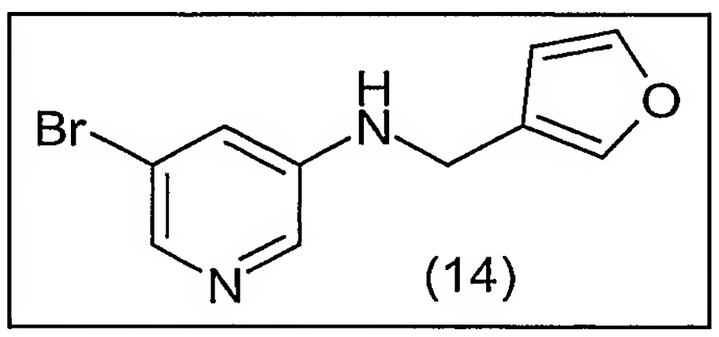
Yield 34.2mg, 38%; $^{\delta}H$ (250MHz, $CDCl_3$) 7.16-7.24 (3H, m), 7.38-7.44 (2H, m) 7.71-7.77 (1H, m), 7.7.86-7.93 (1H, m), 7.99-8.04 (2H, m), 8.24-8.27 (1H, m),8.44-8.45 (1H, m), 8.53-8.56 (2H, m), 9.23-9.24 (1H, m); HPLC 98%; *m/z* (ES) 298 $[M+H]^+$.

Typical example of compound of formula (E), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-(4-chloro-benzyl)-amine* ***(13)***.



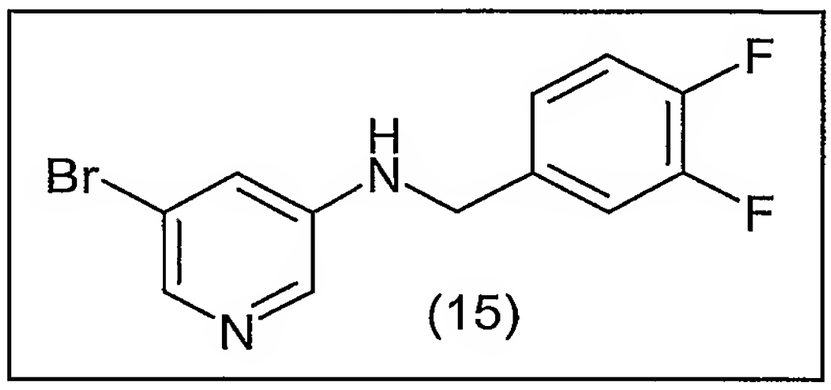
3-Amino-5-bromopyridine (2.04g, 13mmol), 4-chlorobenzaldehyde (1.83g, 13mmol) and sodium triacetoxyborohydride (3.86g, 18.2mmol) in DCM (40ml) was stirred at room temperature for 16h. The reaction was taken up in DCM. The solution was washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant solid was recrystallised from hexane/DCM to afford the desired product (3.14g, 81%) as an off-white solid. ^1H (270MHz, $CDCl_3$) 4.24-4.68(3H, m, NH, CH_2), 6.98-7.00(1H, m, Ar), 7.25-7.36(4H, m, Ar), 7.95-8.02(2H, m, Ar); HPLC: R_t 1.94 (98.70%); *m/z* (ES): 297(100%, M^+).

Typical example of compound of formula (E), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-furan-3-ylmethyl-amine* ***(14)***.



Yield 2.16g, 66%; $^{\delta}$H (250MHz, $CDCl_3$) 4.12-4.16 (3H, m), 6.39-6.40 (1H, m) 7.04-7.06 (1H, m), 7.42-7.43 (2H, m) 7.95-8.01 (2H, m); HPLC 98%; *m/z* (ES) 253 $[M+H]^+$.

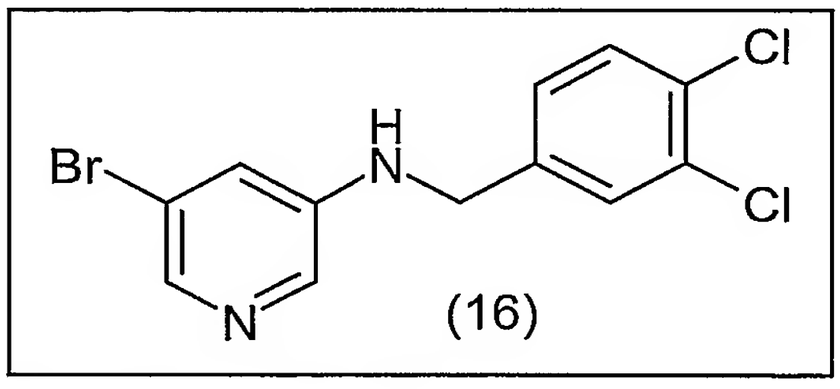
Typical example of compound of formula (E), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-(3,4-difluoro-benzyl)-amine* ***(15)***.



(15)

Yield 2.42g, 62%; $^{\delta}$H (250MHz, $CDCl_3$) 4.30-4.44 (3H, m), 6.97-7.20 (4H, m) 7.95-8.01 (2H, m); HPLC 95%; *m/z* (ES) 299 $[M+H]^+$.

Typical example of compound of formula (E), as described in the general reaction scheme; *(5-bromo-pyridin-3-yl)-(3,4-dichloro-benzyl)-amine* ***(16)***.



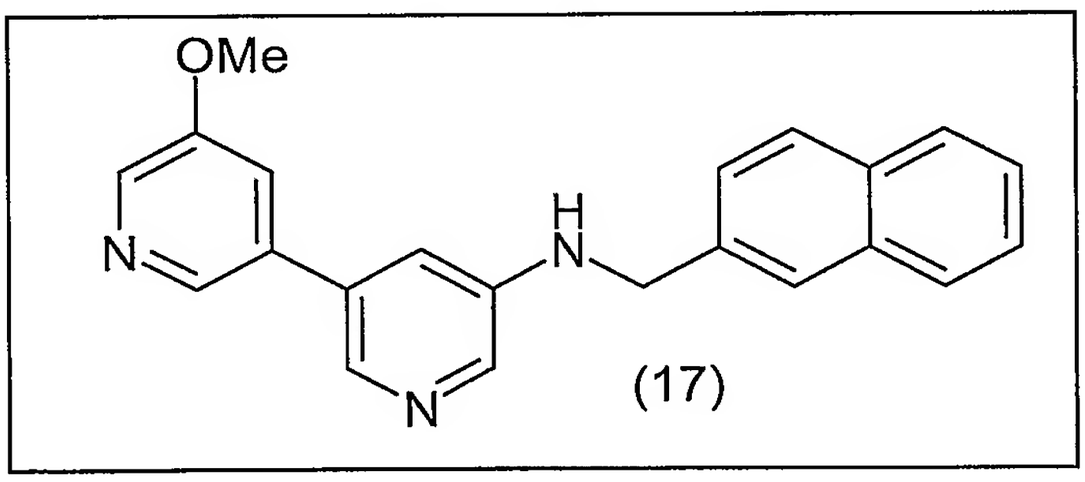
(16)

Yield 2.39g, 55%; $^{\delta}$H (250MHz, $CDCl_3$) 4.30-4.42 (3H, m), 6.97-6.98 (1H, m), 7.13-7.20 (1H, m), 7.39-7.47 (2H, m), 7.92-8.01 (2H, m); HPLC 75%; *m/z* (ES) 331 $[M+H]^+$.

General procedure for the synthesis of compounds of the formula (IIb)

The Suzuki reactions were carried out in stem tubes using a 96 position STEM shaker. To a solution of the required intermediates (E) in DMF (0.3mmol, 0.5ml) was added a solution of boronic acid (Box 4) in DMF (0.36mmol, 0.6ml) and 1.5M Na_2CO_3(aq.) solution (0.75mmol, 0.5ml). The reaction vessels were then placed in a nitrogen filled glovebox for 30min. Two solutions of palladium acetate (95mg) and triphenylphosphine (335mg) in 1,4-dioxane (15ml) were freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml) was added to each reaction vessel inside the glovebox. The vessels were screw capped and then heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative reverse phase HPLC.

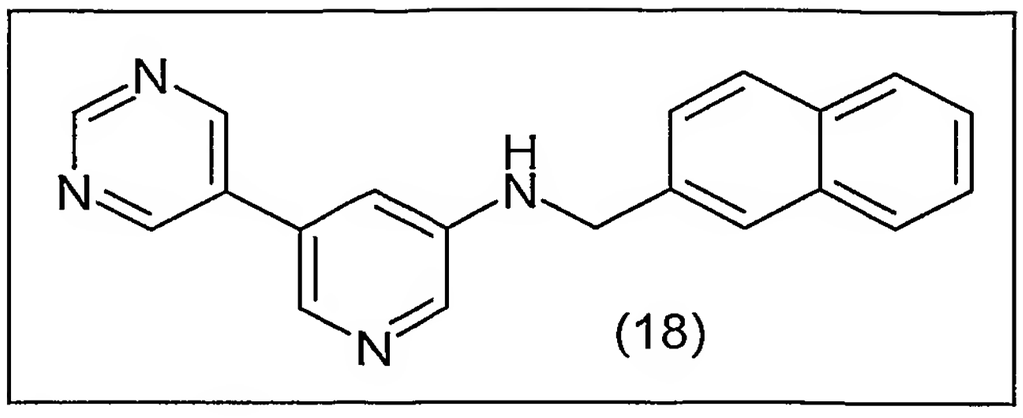
Typical example of compound of formula (IIb), as described in the general reaction scheme; *(5'-methoxy-[3,3']bipyridinyl-5-yl)-naphthalen-2-ylmethyl-amine* ***(17)***.



(17)

Yield 72.4mg, 71%; $^{\delta}H$ (250MHz, $CDCl_3$) 3.83(3H, s), 4.66 (2H, s), 7.24-7.26 (1H, m) 7.40-7.53 (4H, m), 7.79-7.89 (4H, m), 8.11-8.12 (1H, m), 8.34-8.42 (3H, m); HPLC 100%; *m/z* (ES) 342 $[M+H]^+$.

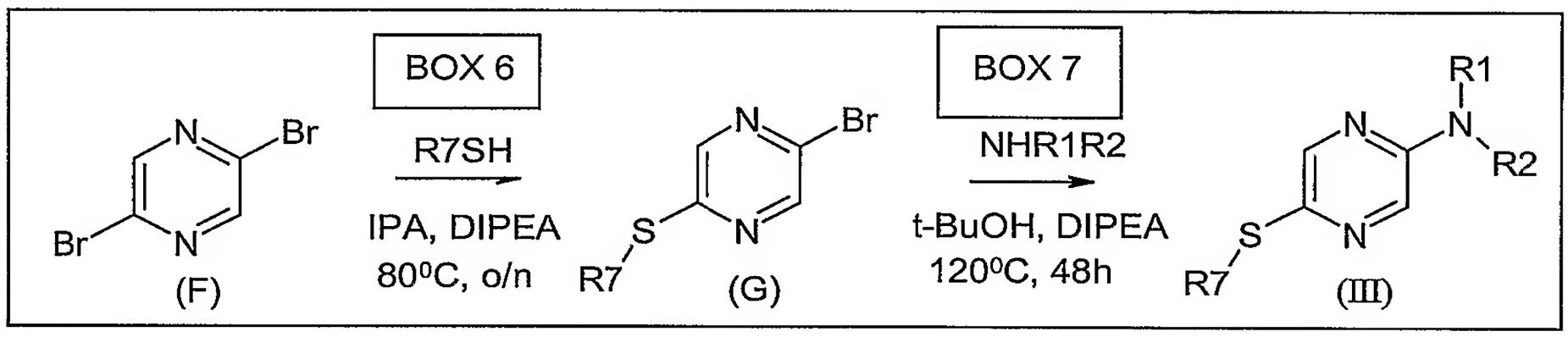
Typical example of compound of formula (IIb), as described in the general reaction scheme; *naphthalen-2-ylmethyl-(5-pyrimidin-5-yl-pyridin-3-yl)-amine* ***(18)***.



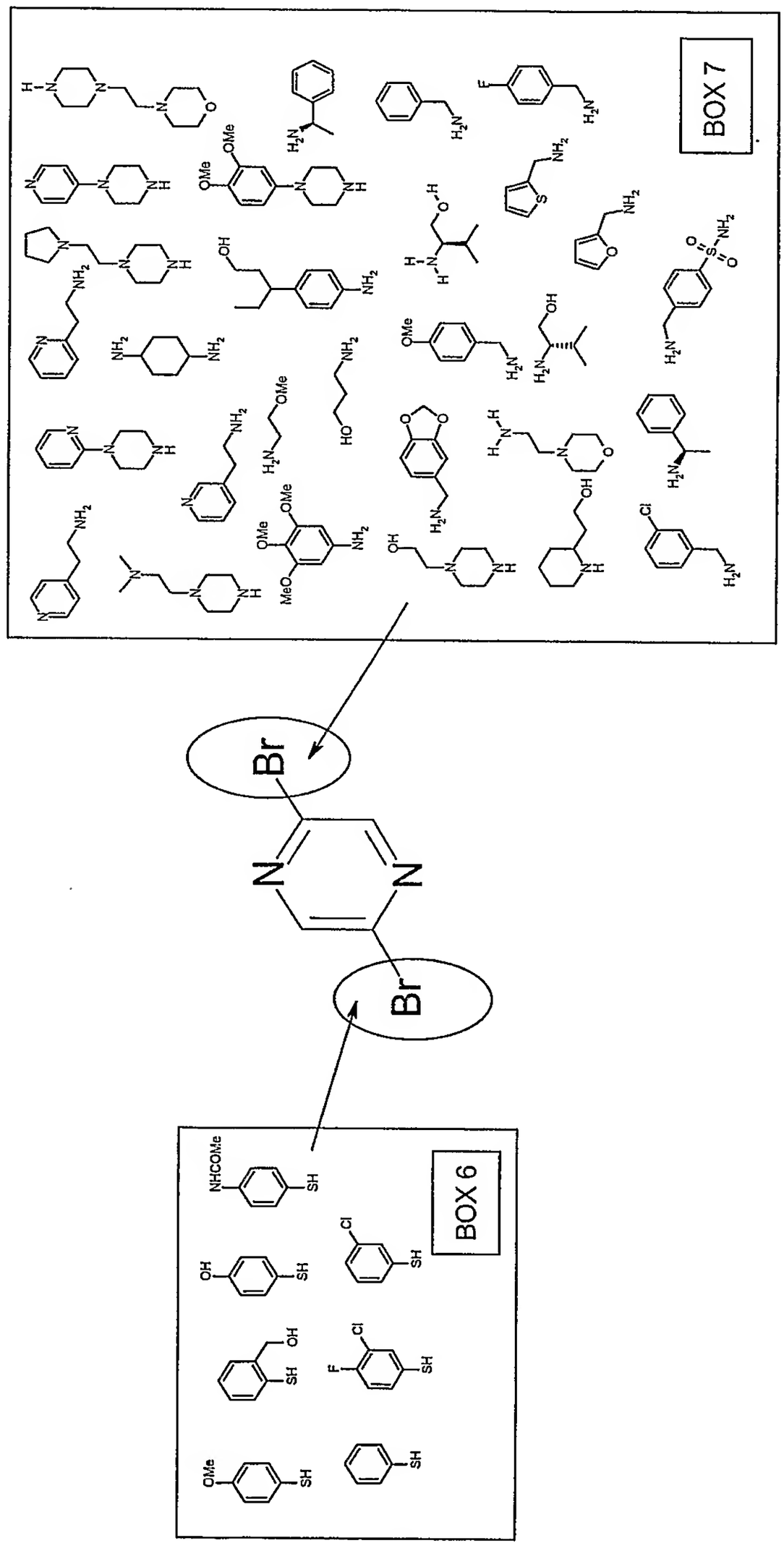
(18)

Yield 66.2mg, 70%; $^{\delta}$H (250MHz, $CDCl_3$) 4.72 (2H, s), 7.13-7.15 (1H, m) 7.62-7.68 (1H, m), 7.78-7.90 (2H, m), 8.20-8.22 (2H, m), 8.30-8.31 (2H, m),8.89 (2H, s), 9.08-9.09 (1H, m), 9.25 (1H, s); HPLC 100%; *m/z* (ES) 314 $[M+H]^+$.

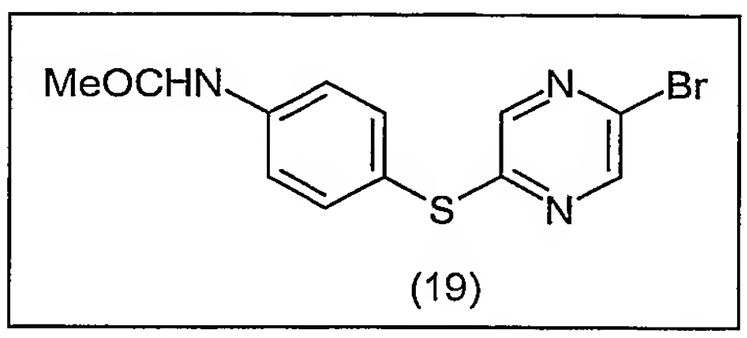
Scheme for synthesising compounds of formula (III) (PS172)



3,6-Dibromopyrazine (F) can undergo thio-etherification with the thiols described in Box 6 to yield compounds with the general structure (G) and then reacted with the amines described in Box 7 to yield final compounds of formula (III).


BOX 7
Br
Br
BOX 6

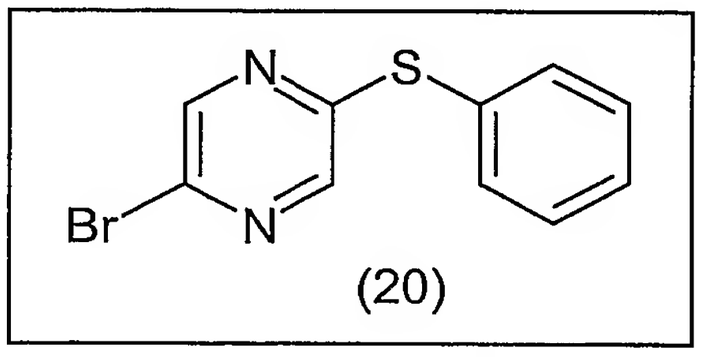
Typical example of compound of formula (G), as described in the general reaction scheme; *N-[4-(5-bromo-pyrazin-2-ylsulfanyl)-phenyl]-acetamide* ***(19)***.



(19)

To a solution of 2,5-dibromopyrazine (PS40), (3.09g, 13mmol) in 2-propanol (6ml) heated at 80°C, was added a solution of 4-acetylamidothiophenol (2.17g, 13mmol) and Hunig's base (2.26ml, 13mmol) in 2-propanol (6ml) dropwise over 6 hours. The reaction mixture was stirred at 80°C overnight. The reaction was followed by HPLC and MS. The reaction was concentrated *in vacuo* and the mixture was dissolved in dichloromethane and washed with water (twice) and brine and dried with magnesium sulphate. The resultant mixture chromatographed (SiO_2, 2% MeOH in hexane) to afford the desired product (4.0g, 95%) as a light brown solid. ^1H (270MHz,CD_3OD) 8.47-8.46 (1H, d, *J*1.47, Ar), 7.92-7.91(1H, d, *J*1.47, Ar), 7.69-7.68(2H, d, *J*2.2, Ar), 7.56-7.55(2H, d, *J*2.2, Ar), 2.14(1H, s, CH_3), HPLC: R_t 2.42 (97.13%); *m/z* (ES): 324(100%, M^+).

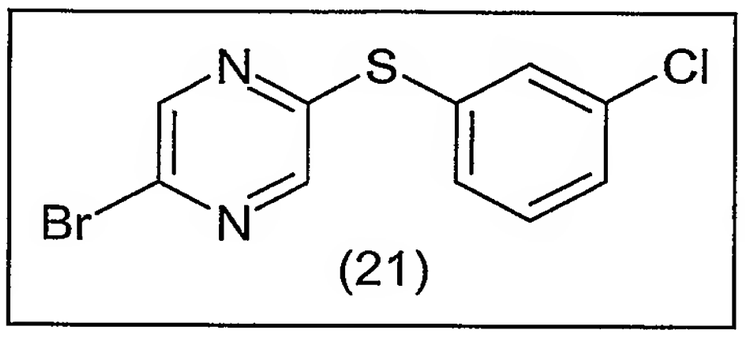
Typical example of compound of formula (G), as described in the general reaction scheme; *2-bromo-5-phenylsulfanyl-pyrazine* ***(20)***.



(20)

Yield 2.21g, 69%; $^{\delta}$H (270MHz, CD_3OD) 7.58-7.61 (3H, m), 7.62-7.63 (2H, m), 7.93-7.94 (1H, d, *J* 1.5), 8.48-8.49 (1H, d, *J* 1.5); HPLC 100%; *m/z* (ES) 267 $[M+H]^+$.

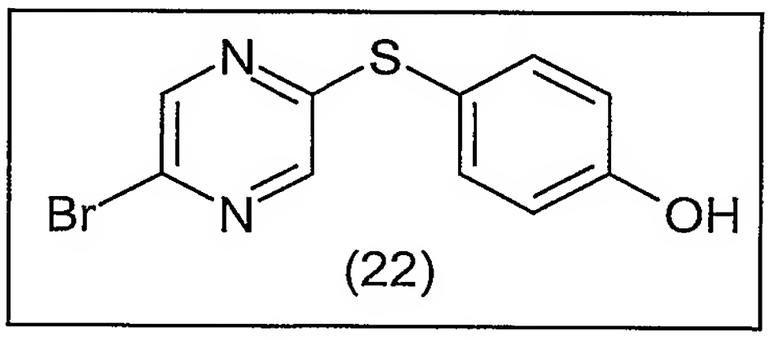
Typical example of compound of formula (G), as described in the general reaction scheme; *2-bromo-5-(3-chloro-phenylsulfanyl)-pyrazine* ***(21)***.



(21)

Yield 2.07g, 86%; $^{\delta}$H (270MHz, CD_3OD) 7.43-7.52 (3H, m), 7.62-7.64 (1H, m), 8.12-8.13 (1H, d, *J* 1.5), 8.51-8.52 (1H, d, *J* 1.5); HPLC 96%; *m/z* (ES) 301 $[M+H]^+$.

Typical example of compound of formula (G), as described in the general reaction scheme; *4-(5-bromo-pyrazin-2-ylsulfanyl)-phenol* ***(22)***.



(22)

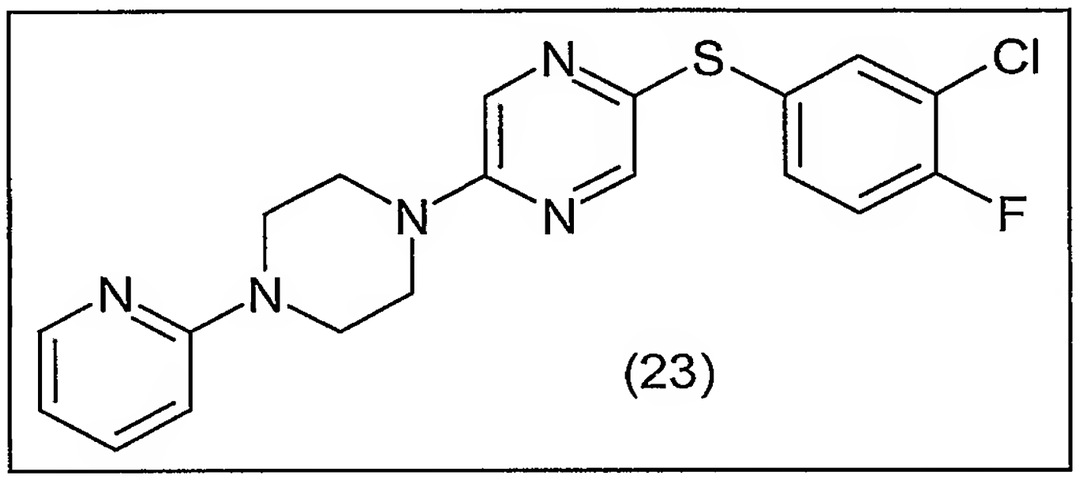
Yield 1.94g, 57%; $^{\delta}$H (270MHz, CD_3OD) 6.87-6.91 (2H, d, *J* 8.8), 7.42-7.45 (2H, d, *J* 8.8), 7.79-7.80 (1H, d, *J* 1.5), 8.46-8.47 (1H, d, *J* 1.5); HPLC 93%; *m/z* (ES) 283 $[M+H]^+$.

<u>General procedure for the synthesis of compounds of the formula (III).</u>

The reactions were performed in 1.5ml Radleys tubes attached to a heater and shaker. To a solution of intermediate (I) in nBuOH (0.3mmol, 0.3ml)

was added a solution of the amine (Box 7) in nBuOH (0.33mmol, 0.2ml) and Hunig's base (0.33mmol, 0.1mL). The reactions were agitated and heated at 120°C for 48h. The reaction mixtures were filtered and purified by preparative HPLC.

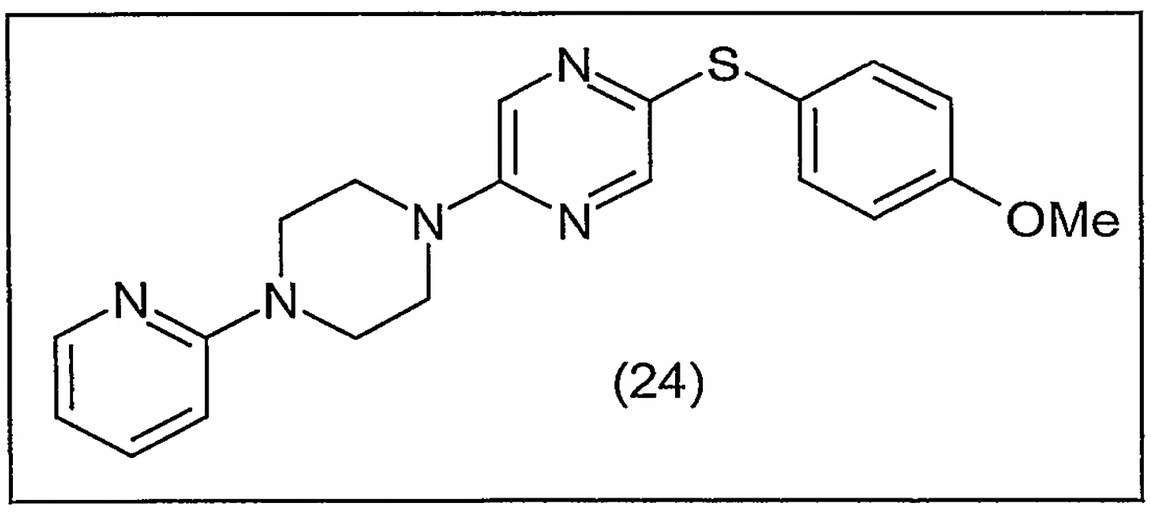
Typical example of compound of formula (III), as described in the general reaction scheme; *5'-(3-chloro-4-fluoro-phenylsulfanyl)-4-pyridin-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl* ***(23)***.



(23)

Yield 63mg, 52%; $^{\delta}$H (250MHz, $CDCl_3$) 3.68-3.80 (8H, m), 6.66-6.71 (2H, m), 7.03-7.10 (1H, m), 7.23-7.29 (1H, m), 7.40-7.44 (1H, m), 7.49-7.57 (1H, m), 8.12-8.24 (3H, m); HPLC 100%; *m/z* (ES) 402 $[M+H]^+$.

Typical example of compound of formula (III), as described in the general reaction scheme; *5'-(4-methoxy-phenylsulfanyl)-4-pyridin-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl* ***(24)***.



(24)

Yield 41.4mg, 36%; $^{\delta}$H (250MHz, $CDCl_3$) 3.69 (8H, s), 3.80 (3H, s), 6.65-6.70 (2H, m), 6.85-6.91 (2H, m), 7.41-7.55 (3H, m), 7.97-7.98 (1H, d, *J* 1.5), 8.06-8.07 (1H, d, *J* 1.5), 8.20-8.23 (1H, m); HPLC 100%; *m/z* (ES) 380 $[M+H]^+$.

Purification Conditions

All compounds have a minimum purity level > 80% as measured by LCMS at 254 nm.

The columns used for the preparative HPLC purification of the various scaffolds are outlined in Table 1:

Table 1

Scaffold	Column
PS40 (Formula I)	Phenomenex Luna 10 μm phenyl-hexyl column (21.2 x 150mm) and Waters SymmetryPrep™ C18 7 μm column (19 x 150mm).
PS81 (Formula II)	Phenomenex Luna 10 μm phenyl-hexyl column (21.2 x 150mm).
PS172 (Formula III)	Waters Xterra® Prep MS C18 5 μm column (19 x 100mm).

The gradient used for PS40 (Formula I) was 95% water (0.2% TFA) / 5% ACN for 1 min to 5% water (0.2 % TFA) / 95% ACN over 8.0 min then held at 5% water (0.2 % TFA) / 95% ACN for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

The gradient used for PS81 (Formula II) was 95% water (0.2% TFA/10% methanol) / 5% ACN (10% methanol) for 1 min to 5% water (0.2 % TFA/10% methanol) / 95% ACN (10% methanol) over 8.0 min then held at 5% water (0.2 % TFA/10% methanol) / 95% ACN (10% methanol) for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

The gradient used for PS172 (Formula III) was 99% water (10mmol NH_3HCO_3) / 1% ACN for 1 min to 9% water (10mmol NH_3HCO_3) / 91% ACN over 8.0 min then held at 9% water (10mmol NH_3HCO_3) / 91% ACN for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

A flow rate of 25 ml/min was used except for PS172 (Formula III) where the main flow was 23.5ml/min and a makeup pump (using ACN only) was used at 1.5ml/min.

The conditions used for the analytical HPLC analysis following preparative HPLC purification are outlined in Table 2:

Table 2

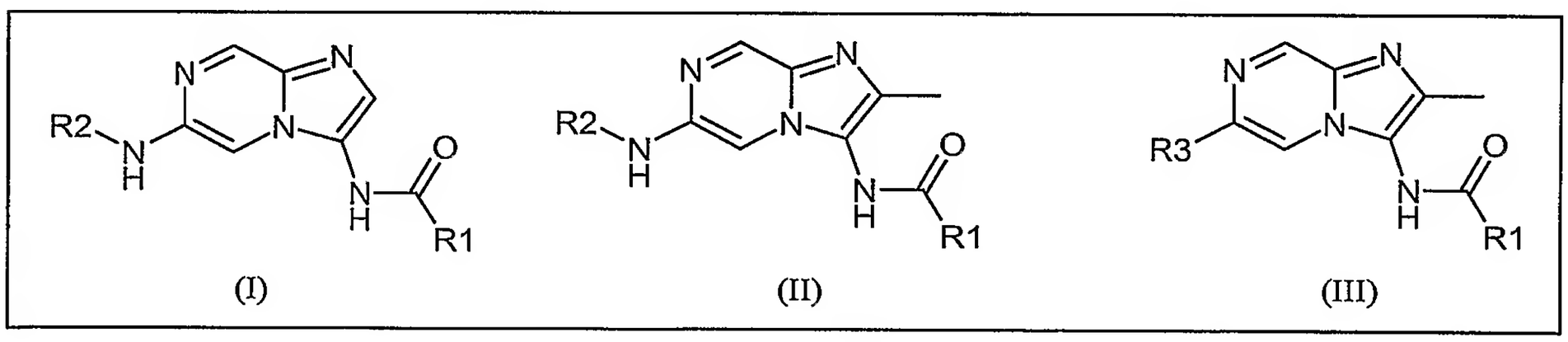
Conditions	Detection
Column: Phenomenex Luna 5 μm C18 (2) 30 × 4.6 mm. **Gradient**: 95% water (0.2% formic acid) / 5% ACN (0.2% formic acid) for 0.5 min then 95% water (0.2% formic acid) / 5% ACN (0.2% formic acid) to 2% water (0.2 % formic acid) / 98% ACN (0.2% formic acid) over 2.8 min. Held at 2% water (0.2 % formic acid) / 98% ACN (0.2% formic acid) for 0.3 min. The solvent mixture is then returned to the initial conditions over 0.1 min and the system allowed to re-equilibrate for 0.2 min. **Flow rate**: 2.0 ml/min. **Temperature**: 30 °C. **Injection volume**: 5 μm partial loop.	UV detection at 254 nm (diode array range 210-280nm). **Electrospray ionisation**: Cone voltage: 25 V. Cone temperature: 20 °C. Source temperature 120 °C. RF lens voltage: 0.0 V. Ion energy: 0.5 eV. Multiplier: 650 V.

LIBRARY SFK10

SFK10 is designed to have primary focus on CDK-4, a key member of the cyclin-dependent kinase family (Hanks' C-M-G-C Group I kinases) with a broader secondary focus on CDK-2 and other members of the family. The central design of the library is based on a novel application of the imidazo[1,2-a]pyrazine scaffold.

A homology model of CDK-4 was developed based on the published crystal structures of CDK-6 and CDK-2 and guided by an existing homology model of CDK-4. Good docking was observed for the imidazo[1,2-a]pyrazine scaffold when this was substituted with 3-amino and 5-amino functions, with a characteristic double H-bond being formed between the backbone Val^{96} of the ATP site of CDK-4 and the 5, ring-6-diaza "amidine" system.

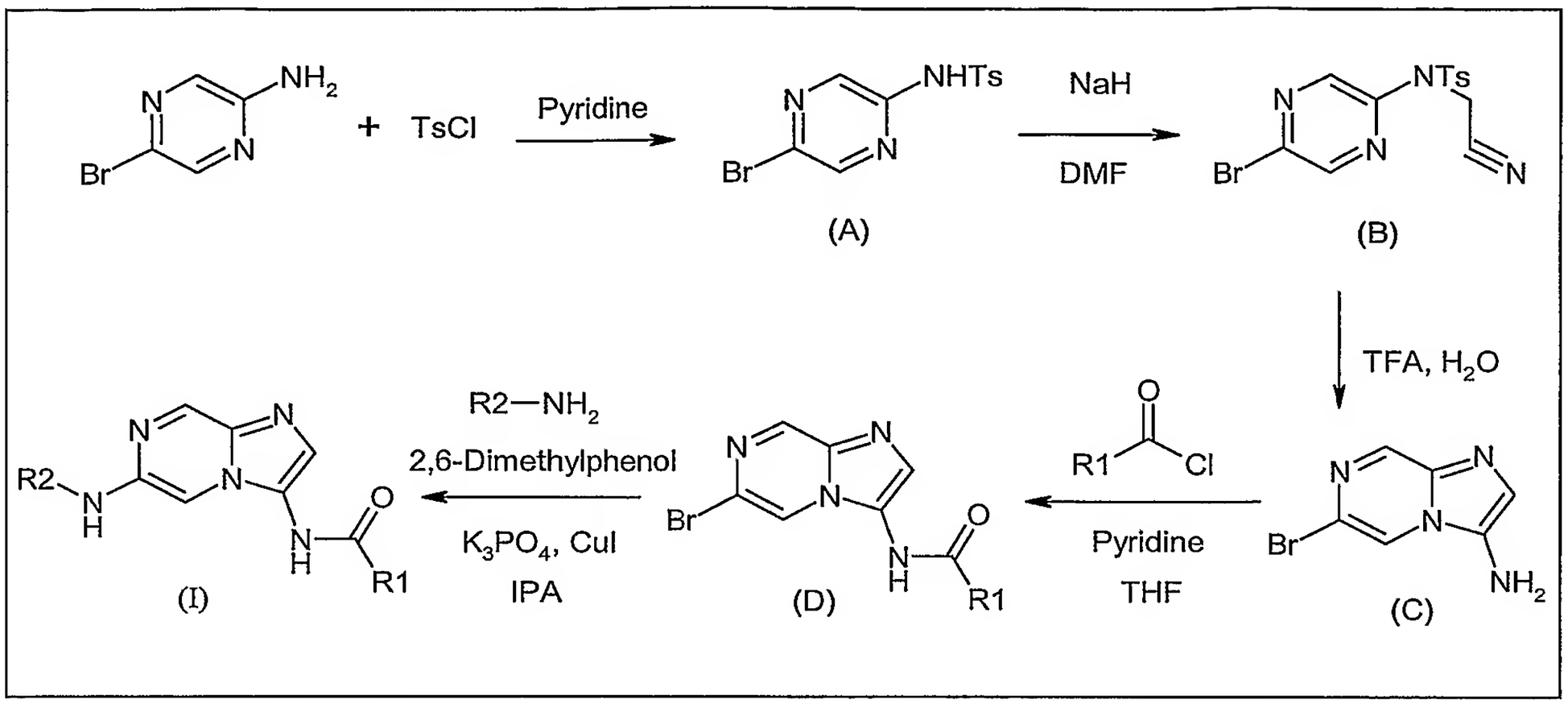
The invention provides a compound library comprising or consisting of a set of structurally related compounds of the general formula (I), (II) and (III):



Wherein R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear

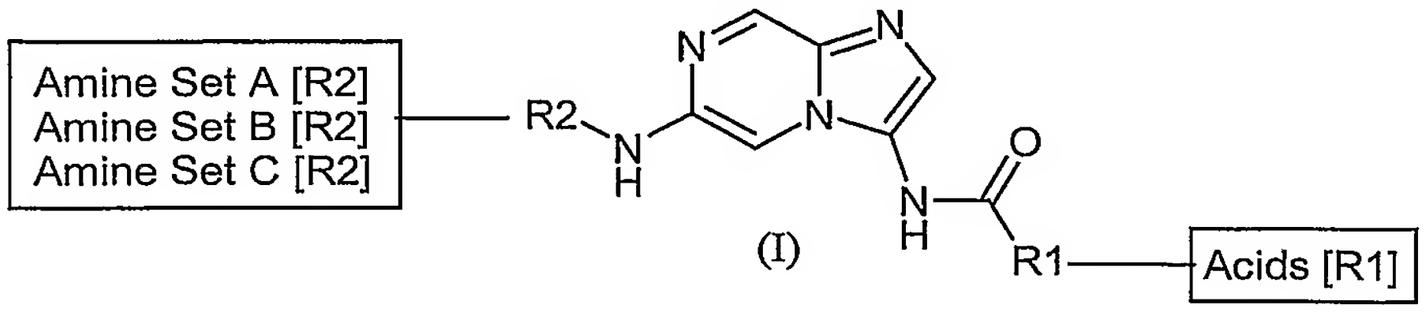
one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; R2 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms and R3 is aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

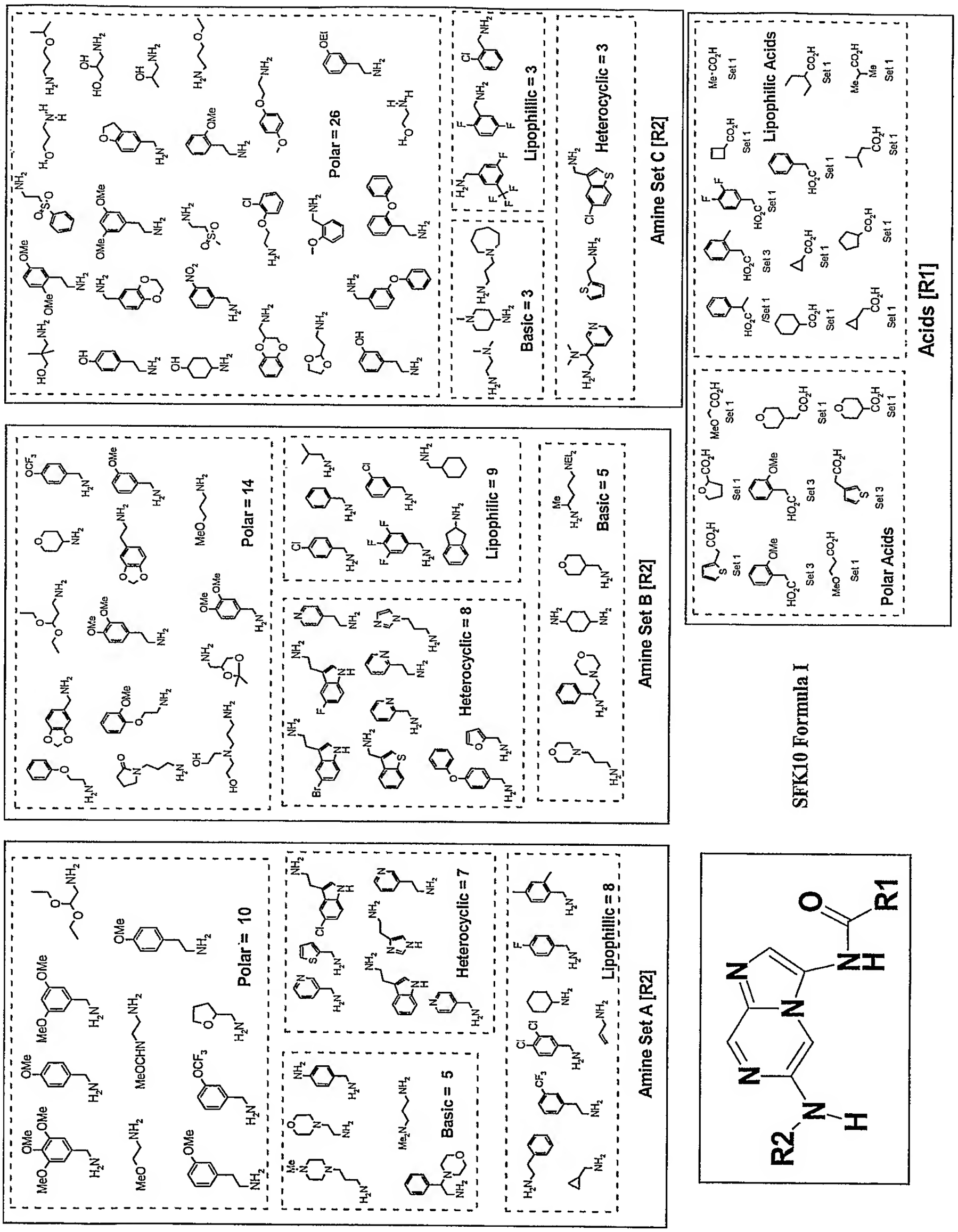
Scheme for synthesising compounds of formula (I)



Compounds of type (C) can be acylated by reaction with the acid chloride derivatives generated from the acids described in the acids box. Compounds of formula (I) are generated from intermediates (D), by reaction with the amines described in the amine sets – amine set A, amine set B and amine set C.

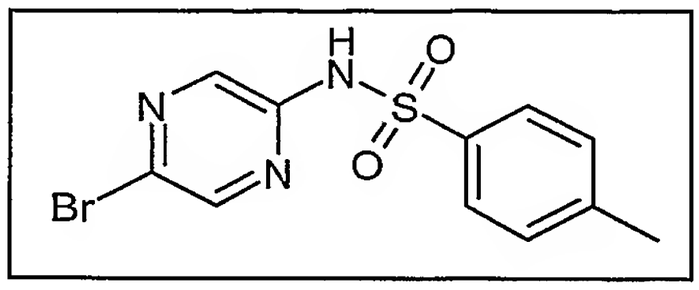
The permitted substituents at positions R1 and R2 are shown in acids [R1], amine set A [R2], amine set B [R2] and acid set C [R2]. The allowed combinations are; compounds of type (D), which are generated from acid set 1, are crossed with amines set A [R2] and amine set C [R2] with the exception of lipophilic acids and lipophilic amines. Compounds of type (D), which are generated from acid set 3, are crossed with amine set A, amine set B and amine set C with the exception of lipophilic acids and lipophilic amines.




Amine Set A [R2]
Polar = 10
Lipophillic = 8
Heterocyclic = 7
Basic = 5
Amine Set B [R2]
Polar = 14
Lipophilic = 9
Heterocyclic = 8
Basic = 5
Amine Set C [R2]
Polar = 26
Lipophilic = 3
Heterocyclic = 3
Basic = 3
Acids [R1]
Polar Acids
Lipophilic Acids
SFK10 Formula I
R1
R2

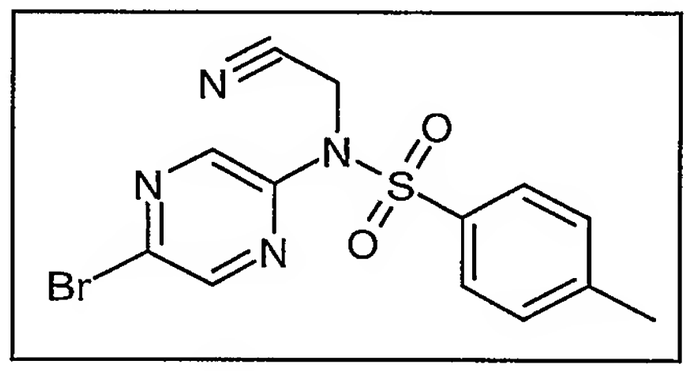
General Procedures:

Synthesis of compound (A), as described in general reaction scheme; *N-(5-bromo-pyrazine-2-yl)-4-methyl-benzenesulfonamide.*



To a stirred solution of 5-bromo-pyrazin-2-ylamine (60 g, 0.34 mol) in pyridine (600 ml) was added tosyl chloride (73.2 g, 0.38 mol). The reaction was stirred at room temperature for 18h then concentrated *in vacuo*. The residue was triturated (dichloromethane : methanol, 1 : 1) to give compound (A) (87.6 g, 79%). δ_H (270 MHz, $CDCl_3$) 2.49 (s, 3H), 7.54 (d, *J* 8.1, 2H), 8.01 (d, *J* 8.3, 2H), 8.32 (d, *J* 1.5, 1H), 8.57 (d, *J* 1.5, 1H); HPLC 97%.

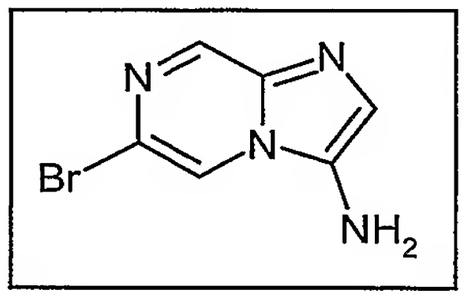
Synthesis of compound (B), as described in general reaction scheme; *N-(5-bromo-pyrazin-2-yl)-N-cyanomethyl-4-methyl-benzenesufonamide.*



Compound (A) (60 g, 0.19 mol) was added in portions to a suspension of sodium hydride (60% in mineral oil, 8.7 g, 0.22 mol), in DMF (500 ml) over a period of 30 minutes. The mixture was stirred at room temperature for 30 minutes before the addition of bromoacetonitrile (15 ml, 0.23 mol) over a further 30 minutes. The reaction was heated at 60°C for three hours then stirred for 18h at room temperature. After this time the

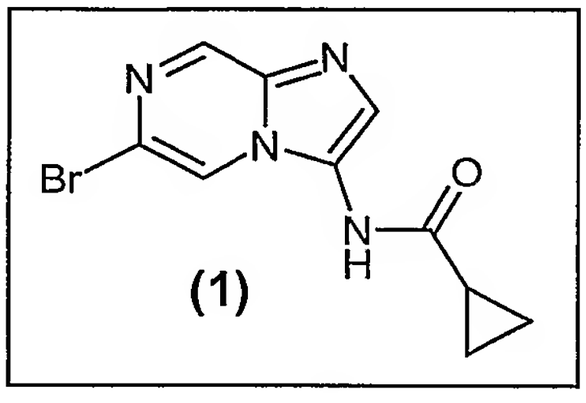
reaction was concentrated *in vacuo* and the residue was purified by trituration with methanol to give compound (B) (49 g, 68%). δ_H (270 MHz, $CDCl_3$) 2.41 (s, 3H), 4.68 (s, 2H), 7.42 (d, *J* 8.1, 2H), 7.71 (d, *J* 8.1, 2H), 8.41 (d, *J* 1.2, 1H), 8.92 (d, *J* 1.2, 1H); HPLC 95%.

Synthesis of compound (C), as described in general reaction scheme; *6-bromo-imidazo[1,2-a]pyrazin-3-ylmine.*



A solution of compound (B) (49 g, 0.13) in a mixture of trifluoroacetic acid (360 ml) and water (40 ml) was heated at 40°C for 1 hour. Toluene (2 × 250 ml) was then added and the mixture concentrated *in vacuo*. The residue was treated with an aqueous solution of sodium acetate (40 g, 150 ml) and stirred for 1h at 0°C. The product was collected by filtration and washed with cold water to give compound (C) (25 g, 85%). δ_H (270 MHz, $CDCl_3$) 6.03 (br s, 2H), 7.27 (s, 1H), 8.52 (d, *J* 1.2), 8.72 (d, *J* 1.2, 1H); *m/z* (APCI) 213 (M^+); HPLC 91%

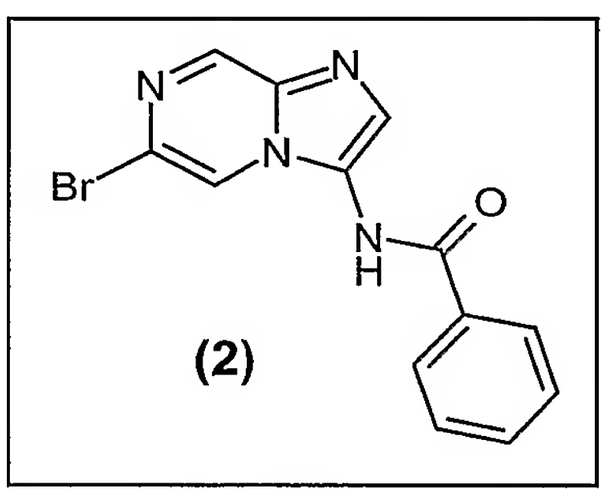
Typical example of compound of formula (D), as described in general reaction scheme; *cyclopropanecarboxylic acid (6-bromo-imidazo[1,2-a]pyrazin-3-yl)-amide* ***(1).***



(1)

To a suspension of 6-bromo-imidazo[1,2-a]pyrazin-3-ylmine (C) (2.0 g, 9.4 mmol) in THF (50 ml) was added pyridine (1.5 ml, 18.6 mmol) followed by cyclopropane carbonyl chloride (1.1 g, 10.3 mmol). The reaction was heated at 50°C for 3h then the solvent was removed *in vacuo*. A mixture of ethyl acetate (75 ml) and a saturated solution of $NaHCO_3$ (75 ml) were added to the residue, which resulted in precipitation of a solid. The solid was collected by filtration and washed with water then ethyl acetate to give the desired product as a light brown solid (1.9 g, 72%). δ_H (250 MHz, DMSO) 0.89 (m, 4H), 1.9 (m, 1H), 2.49 (m, 1H), 7.85 (s, 1H), 8.56 (d, *J* 1.2 1H), 8.84 (d, *J* 1.2, 1H), 10.8 (s, 1H); *m/z* (APCI) 218 (M^+); HPLC 96%.

Typical example of compound of formula (D), as described in general reaction scheme; *N-(6-bromo-imidazo[1,2-a]pyrazin-3-yl)-2-methyl-benzeamide* ***(2)***.

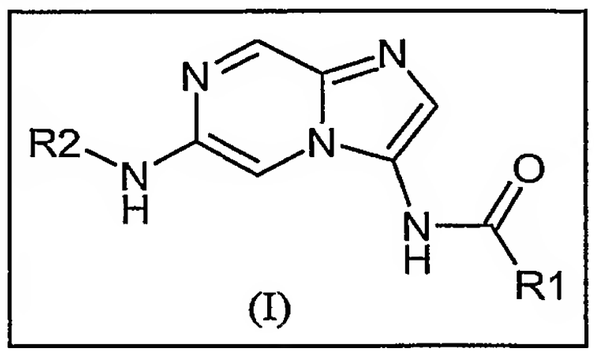


(2)

To a solution of *o*-tolylacetic acid (18.02 g, 120 mmol) in CH_2Cl_2 (200 ml) was added oxalyl chloride (32 ml, 360 mmol) followed by DMF (3 drops). The reaction was stirred at room temperature for 3h then concentrated *in vacuo*. The residue was dissolved in THF (50 ml) then added to a suspension of compound (C) in THF (150 ml) and pyridine (9.7 ml, 120 mmol). The mixture was heated at 50°C for 30 mins. After this time the reaction was concentrated *in vacuo* and a mixture of ethyl acetate (250 ml) and a saturated solution of $NaHCO_3$ (250 ml) was added. This resulted in the formation of a solid, which was collected by filtration to give the

desired compound as a brown solid (16.4 g, 79%). δ_H (250 MHz, DMSO) 2.3 (s, 3H), 3.86 (s, 2H), 7.12-7.16 (m, 3H), 7.27-7.30 (m, 1H), 7.87 (s, 1H), 8.76 (d, *J* 1.2, 1H), 8.87 (d, *J* 1.2 1H); *m/z* (APCI) 345 (M^+); HPLC 100%.

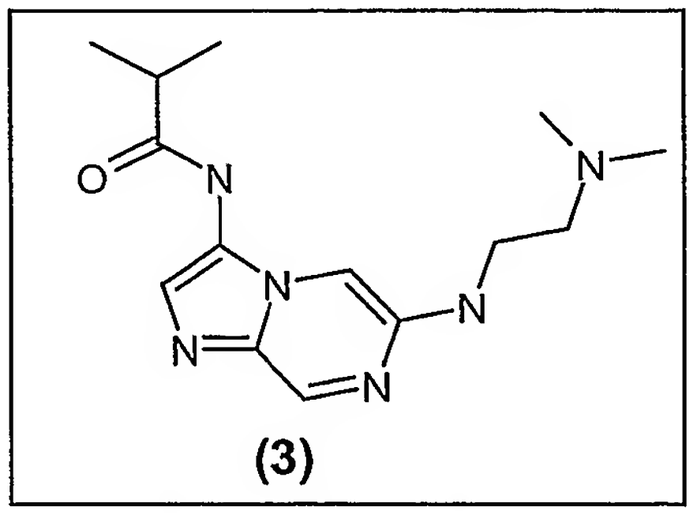
General Procedure for the synthesis of compounds of formula (I)



(I)

The reactions were carried out in stem tubes with a 96 well stem shaker. Each tube was charged with a compound of formula (D) (0.3 mmol), followed by the addition of propan-2-ol (0.75 ml), a solution of the amine in propan-2-ol (0.6 mmol, 0.25 ml), a solution of 2,6-dimethylphenol in propan-2-ol (0.24 mmol, 0.25ml), potassium phosphate (0.6 mmol), and copper iodide (0.06 mmol). The reaction vessels were flushed with nitrogen then heated at 80°C for 22h. After this time the reactions were filtered then purified by preparative HPLC.

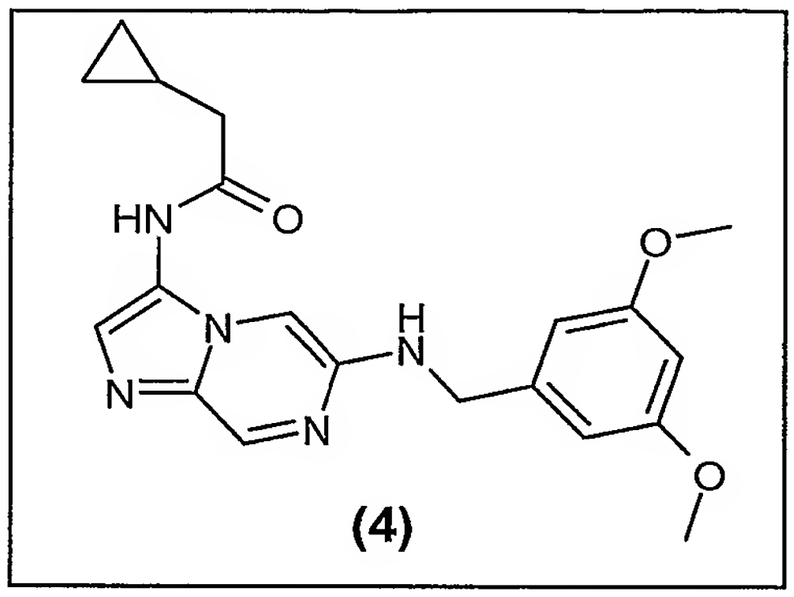
Typical example of compound of formula (I); *N-[6-(2-dimethylamino-ethylamino)-imidazo [1,2-a]pyrazin-3-yl]isobutyramide* ***(3)***.



(3)

Yield 41.3 mg, 47%; *m/z* (ES) 291 $(M+1)^+$; HPLC 100%.

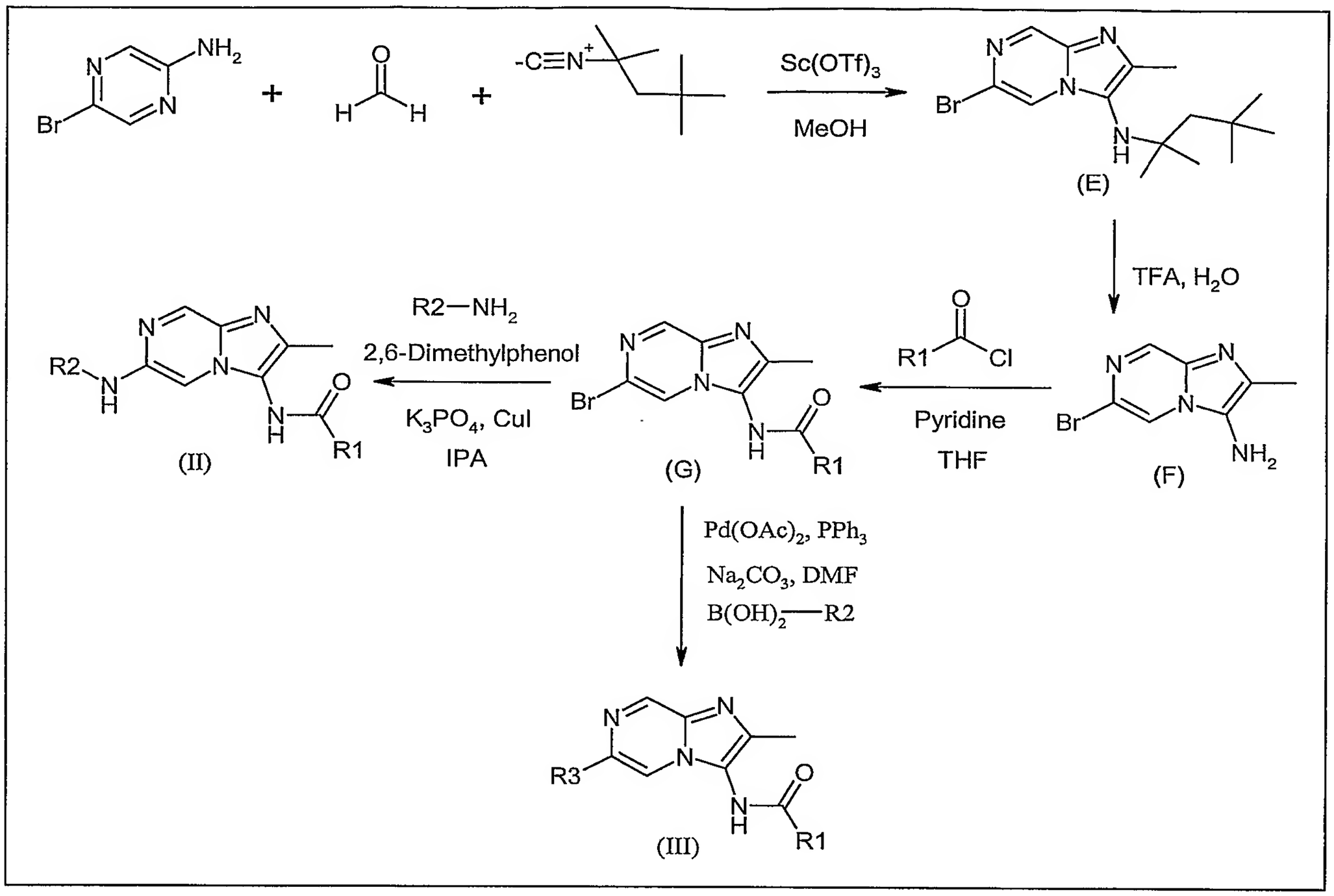
Typical example of compound of formula (I); *2-cyclopropyl-N-[6-(3,5-dimethoxy-benzyl amino)-imidazo[1,2-a]pyrazin-3-yl]-acetamide* ***(4)***.



(4)

Yield 30.9 mg, 27%; *m/z* (ES) 382 $(M+1)^+$; HPLC 100%.

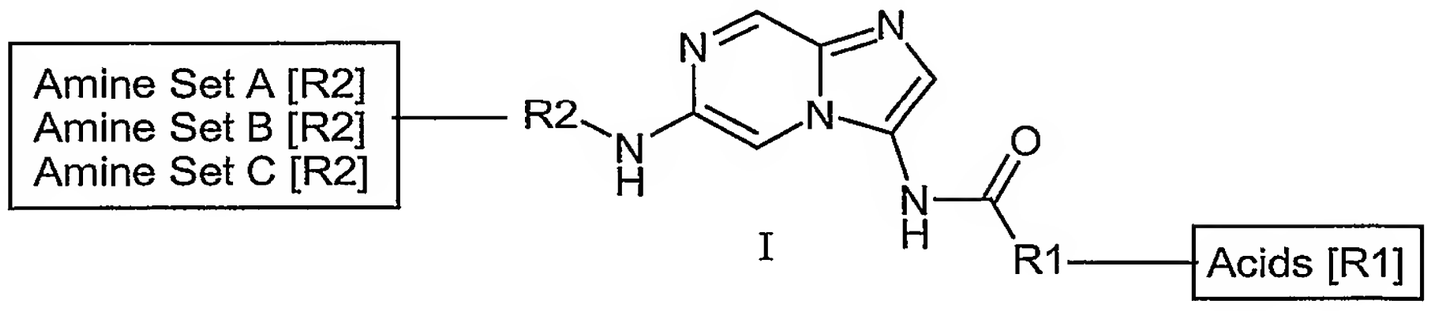
Scheme for synthesising compounds of formula (II) and (III)



Compounds of type (F) can be acylated by reaction with acid chloride derivatives generated from the acids described in the acids Box. Compounds of formula (II) are generated from intermediates (G) by reaction with amines described in the amine sets – amine set A, amine set B and amine set C.

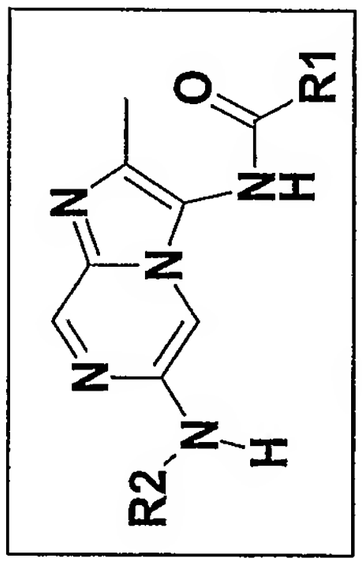
The permitted substituents at positions R1 and R2 are shown in acids [R1], amine set A [R2], amine set B [R2] and amine set C [R2]. The allowed combinations are; compounds of type (G), which are generated from acid set 1, are crossed with amines set B [R2] with the exception of lipophilic acids and lipophilic amines. Compounds of type (G), which are generated from acid set 2, are crossed with amine set C with the exception of lipophilic acids and lipophilic amines. Compounds of type (G), which are

generated from acid set 3, are crossed with amine set C with the exception of lipophilic acids and lipophilic amines.



I

SFK10 Formula II



Acids [R1]

Polar Acids

Lipophilic Acids

Amine Set A [R2]

Polar = 10

Basic = 5

Heterocyclic = 7

Lipophilic = 8

Amine Set B [R2]

Polar = 14

Basic = 5

Heterocyclic = 8

Lipophilic = 9

Amine Set C [R2]

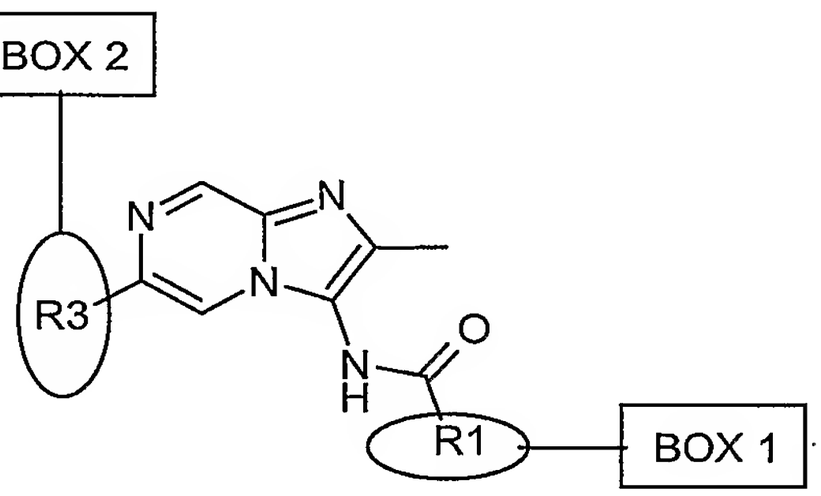
Polar = 26

Basic = 3

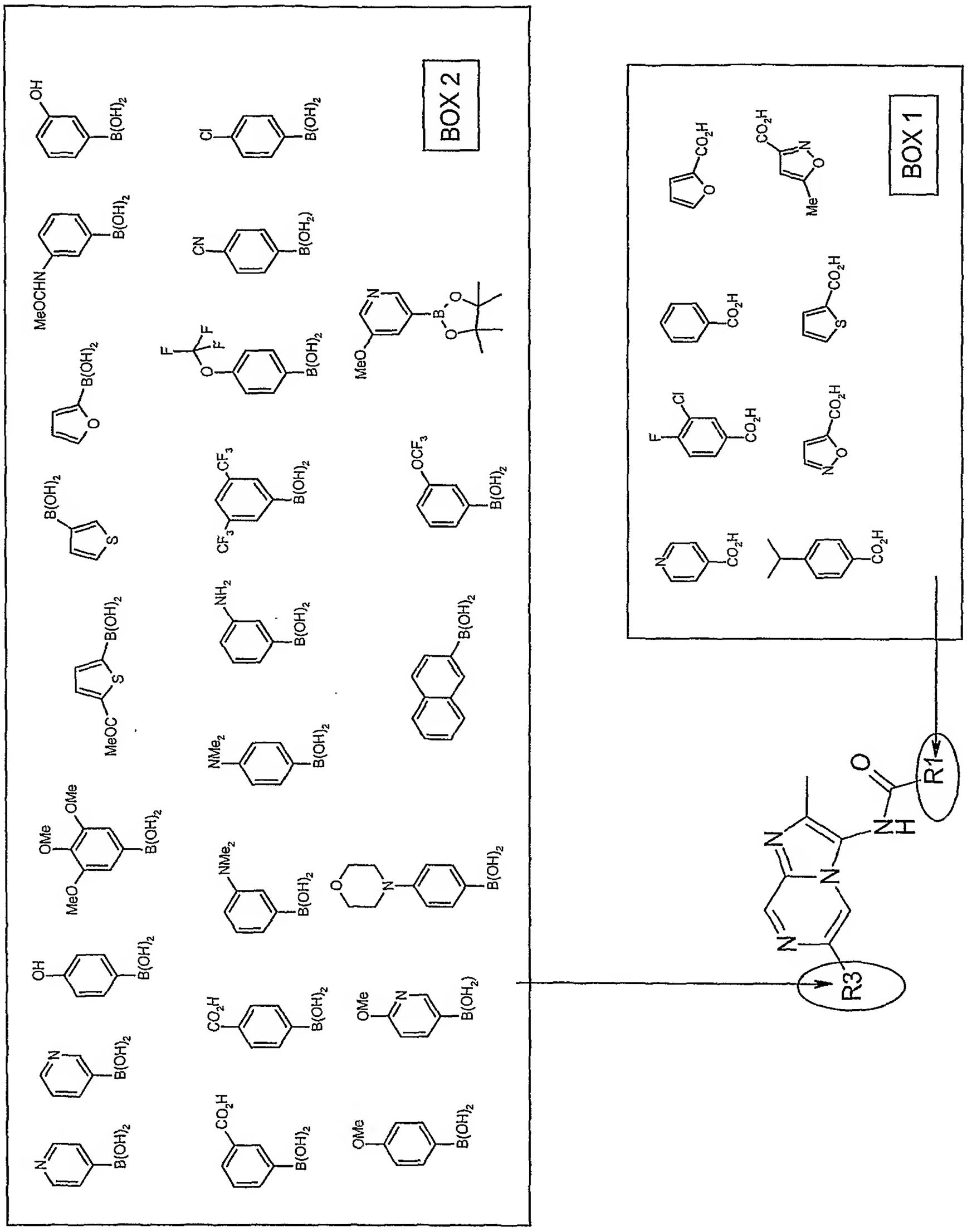
Heterocyclic = 3

Lipophilic = 3

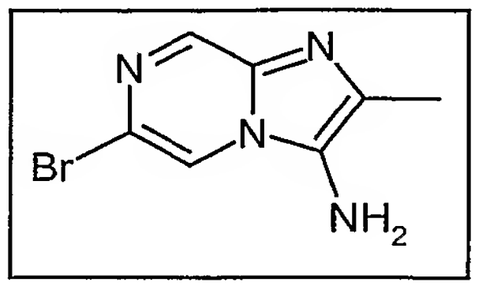
Compounds of type (F) can be acylated by reaction with acid chloride derivatives generated from the acids described in Box 1. Compounds of formula (III) are generated from intermediates (G) by reaction with the boronic acid reagents described in Box 2.



SFK10 Formula (III)



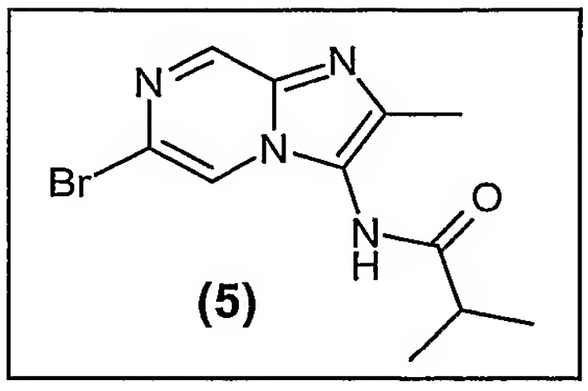
Synthesis of compound (F) as described in the general reaction scheme; *6-bromo-2-methyl-imidazo[1,2-a]pyrazin-3-ylamine.*



To a solution of 5-bromo-pyrazin-2-ylamine (34.6 g, 0.202 mol) in methanol was added acetaldehyde (27.9 ml, 0.5 mol) followed by $Sc(OTf)_3$ (5 g, 10.1 mmol). The mixture was stirred at room temperature for 1h before the addition of *tert*-octyl isocyanide (40 ml, 0.224 mol). The reaction was stirred at room temperature for 16h then the solvent was removed *in vacuo*. The residue was partitioned between a saturated solution of $NaHCO_3$ (500 ml) and ethyl acetate (750 ml). The organic phase was separated, dried ($MgSO_4$) then concentrated to give the crude product (E). δ_H (270 MHz, $CDCl_3$) 1.10 (m, 17H), 2.47 (s, 3H), 8.20 (d, *J* 1.2, 1H), 8.64 (d, *J* 1.2, 1H); *m/z* (APCI) 339 [M^+].

Compound (E) was dissolved in dichloromethane (100 ml) and TFA (100 ml) was added and the mixture was stirred for 1h. After this time the reaction was adjusted to pH 11 with an aqueous solution of 5M NaOH, which resulted in the precipitation of a solid. The solid was collected by filtration and washed with ethyl acetate to give the desired product (F) (37 g, 81%). δ_H (250 MHz, DMSO) 2.31 (s, 3H), 5.71 (br s, 2H), 8.27 (d, *J* 1.1, 1H), 8.41 (d, *J* 1.1, 1H); *m/z* (APCI) 227 [M^+]; HPLC 96%.

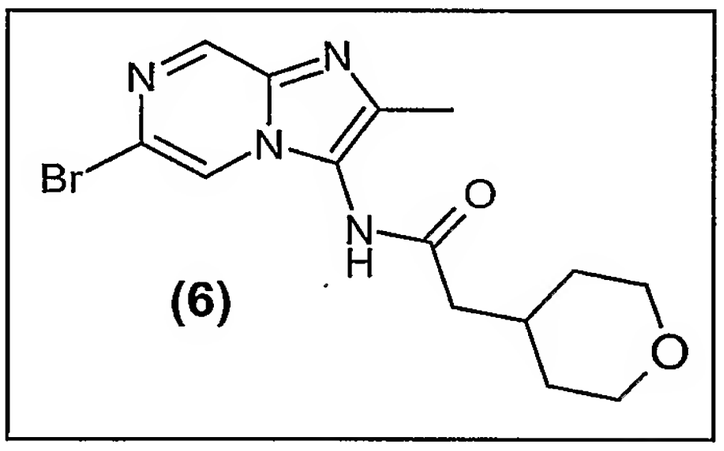
Typical example of compound of formula (G), as described in general reaction scheme; *N-(6-bromo-2-methyl-imidazo[1,2-a]pyrazine-3-yl)-isobutyramide* ***(5)***.



(5)

To a suspension of compound (F) (1.14 g, 5 mmol) in THF (50 ml) was added pyridine (0.82 ml, 10 mmol) followed by *iso*-buturyl chloride (0.8 ml, 7.5 mmol). The reaction was heated at 50°C for 4h. The reaction was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc MeOH, 95 : 5) to give the desired product as a brown solid (0.67 g, 45%). δ_H (250 MHz, DMSO) 0.97 (d, *J* 6.1, 3H), 2.05-2.17 (m, 1H), 2.30 (s, 3H), 8.29 (d, *J* 1.3, 1H), 8.77 (d, *J* 1.3, 1H), 10.08 (s, 1H); *m/z* (APCI) 297 (M^+); HPLC 99%.

Typical example of compound of formula (G), as described in general reaction scheme; *N-(6-bromo-2-methyl-imidazo[1,2-a]pyrazin-3-yl)-2-(tetrahydro-pyran-4-yl)-acetamide* ***(6)***.

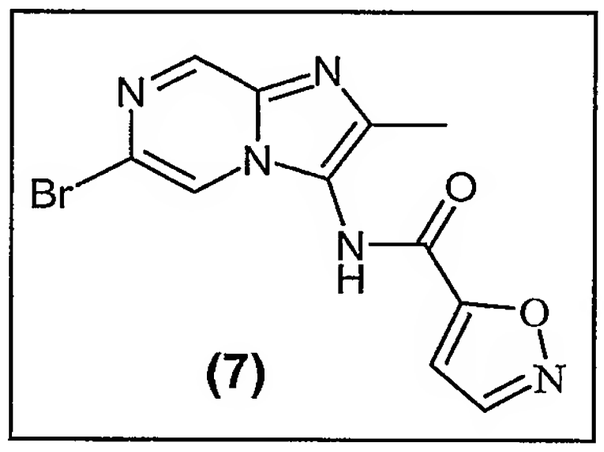


(6)

To a solution of tetrahydropyran-4-ylacetic acid (5 g, 35 mmol) in DCM (70 ml) was added oxalyl chloride (4.6 ml, 52.5 mmol) dropwise followed by DMF (2 drops) and the mixture was stirred at room temperature for 3h. After this time the reaction was concentrated *in vacuo* and the residue was dissolved in THF (25 ml) then added to a suspension of compound (F) (5.67 g, 25 mmol) in THF (50 ml) and pyridine (4 ml, 50 mmol). The reaction was heated at 50°C for 4h then concentrated *in vacuo*. A mixture

of a saturated aqueous solution of $NaHCO_3$ (150 ml) followed by ethyl acetate (150 ml) was added to the residue, which resulted in the formation of a solid. The solid was collected by filtration, which was washed with ethyl acetate to give the desired product as an off white solid (4.81 g, 55%). δ_H (250 MHz, DMSO) 1.30-1.36 (m, 2H), 1.60-1.66 (m, 2H), 1.97-2.03 (m, 1H), 2.29 (s, 3H), 2.39 (d, *J* 7.5, 2H), 3.26-3.31 (m, 2H), 3.81-3.87 (m, 2H), 8.32 (d, *J* 1.2 1H), 8.77 (d, *J* 1.2, 1H), 10.11 (s, 1H); *m/z* (APCI) 353 (M^+); HPLC 99%.

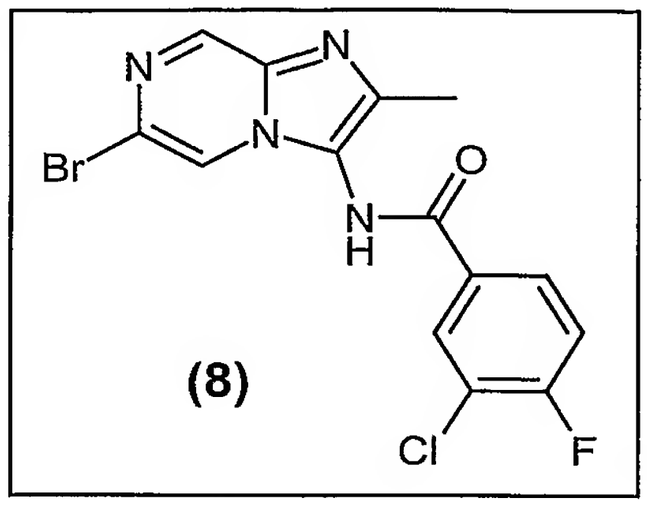
Typical example of compound of formula (G), as described in general reaction scheme; *isoxazole-5-carboxylic acid (6-bromo-2-methyl-imidazo[1,2-a]pyrazin-3-yl)-amide* ***(7)***.



(7)

To a suspension of compound (F) (3.0 g, 13.2 mmol) in THF (75 ml) and pyridine (2.1 ml, 26.4 mmol) was added isoxazole-5-carbonyl chloride (2.2 g, 16.5 mmol) and the reaction was heated at 50°C for 2h. After this time the reaction was concentrated *in vacuo* and a mixture of a saturated aqueous solution of $NaHCO_3$ (100 ml) followed by ethyl acetate (100 ml) was added to the residue, which resulted in the formation of a solid. The solid was collected by filtration and washed with ethyl acetate to give the desired product as a brown solid (3.5 g, 83%). δ_H (250 MHz, DMSO) 2.35 (s, 1H), 7.31 (d, *J* 1.9, 1H), 8.73 (d, *J* 1.3, 1H), 8.83 (d, *J* 1.3, 1H), 8.86 (d, *J* 1.9, 1H), 11.13 (s, 1H); *m/z* (APCI) 322 (M^+); HPLC 99%.

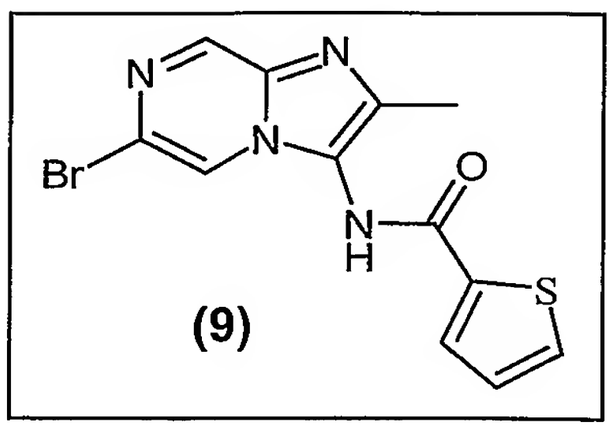
Typical example of compound of formula (G), as described in general reaction scheme; *N-(6-bromo-2-methyl-imidazo[1,2-a]pyrazin-3-yl)-3-chloro-4-floro-benzamide* ***(8)***.



(8)

To a suspension of compound (F) (3.0 g, 13.2 mmol) in THF (75 ml) and pyridine (2.1 ml, 26.4 mmol) was added 3-chloro-4-fluorobenzyl chloride (3.2 g, 16.5 mmol) and the reaction was heated at 50°C for 2h. After this time the reaction was concentrated *in vacuo* and a mixture of a saturated aqueous solution of $NaHCO_3$ (100 ml) followed by ethyl acetate (100 ml) was added to the residue, which resulted in the formation of a solid. The solid was collected by filtration and washed with ethyl acetate to give the desired product as a brown solid (3.8 g, 75%). δ_H (250 MHz, DMSO) 2.35 (s, 1H), 7.63 (t, *J* 8.9, 1H), 8.03-8.10 (m, 1H), 8.28-8.32 (m, 1H), 8.65 (d, *J* 1.1, 1H), 8.81 (d, *J* 1.1, 1H), 10.84 (s, 1H); *m/z* (APCI) 383 (M^+); HPLC 98%.

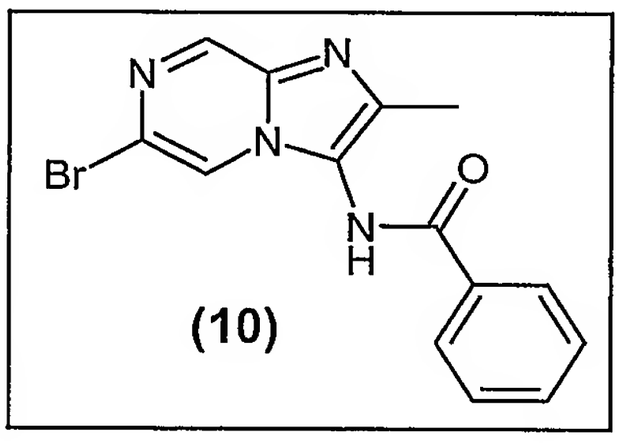
Typical example of compound of formula (G), as described in general reaction scheme; *thiophene-2-carboxylic acid (6-bromo-2-methyl-imidazo[1,2-a]pyrazin-3-yl)-amide* ***(9)***.



(9)

To a suspension of compound (F) (4.5 g, 20.0 mmol) in DCM (200 ml) and pyridine (3.2 ml, 40 mmol) was added 2-thiophene carbonylchloride (2.15 ml, 20 mmol) and the reaction was heated at 50°C for 2h. After this time the reaction was concentrated *in vacuo* and a mixture of a saturated aqueous solution of $NaHCO_3$ (150 ml) followed by ethyl acetate (150 ml) was added to the residue, which resulted in the formation of a solid. The solid was collected by filtration and washed with ethyl acetate to give the desired product as a brown solid (3.0 g, 45%). δ_H (250 MHz, DMSO) 2.35 (s, 1H), 7.28 (dd, *J* 3.9, 4.9, 1H), 7.94 (d, *J* 4.9, 1H), 8.06 (d, *J* 3.0, 1H), 8.58 (d, *J* 1.2, 1H), 8.82 (d, *J* 1.2, 1H), 10.63 (s, 1H); *m/z* (APCI) 337 (M^+); HPLC 94%.

Typical example of compound of formula (G), as described in general reaction scheme; *N-(6-bromo-2-methyl-imidazo[1,2-a]pyrazine-3-yl)-benzamide* ***(10)***.

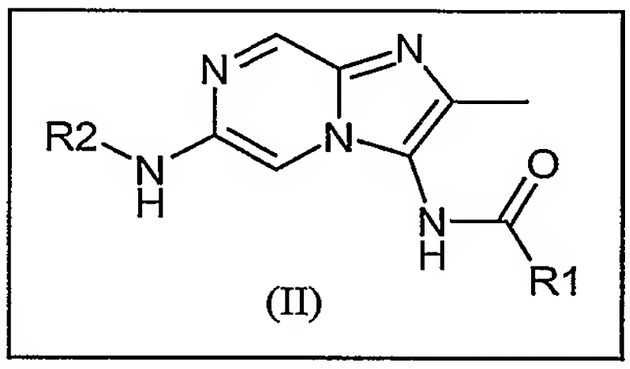


(10)

To a suspension of compound (F) (3.0 g, 13.2 mmol) in THF (75 ml) and pyridine (2.1 ml, 26.4 mmol) was added benzoyl chloride (2.1 ml, 16.5 mmol) and the reaction was heated at 50°C for 2h. After this time the

reaction was concentrated *in vacuo* and a mixture of a saturated aqueous solution of $NaHCO_3$ (100 ml) followed by ethyl acetate (100 ml) was added to the residue, which resulted in the formation of a solid. The solid was collected by filtration and washed with ethyl acetate to give the desired product as a brown solid (3.7 g, 84%). δ_H (250 MHz, DMSO) 2.36 (s, 1H), 7.53-7.68 (m, 3H), 8.04-8.08 (m, 2H), 8.57 (d, *J* 1.3, 1H), 8.82 (d, *J* 1.3, 1H), 10.63 (s, 1H); *m/z* (APCI) 331 (M^+); HPLC 91%.

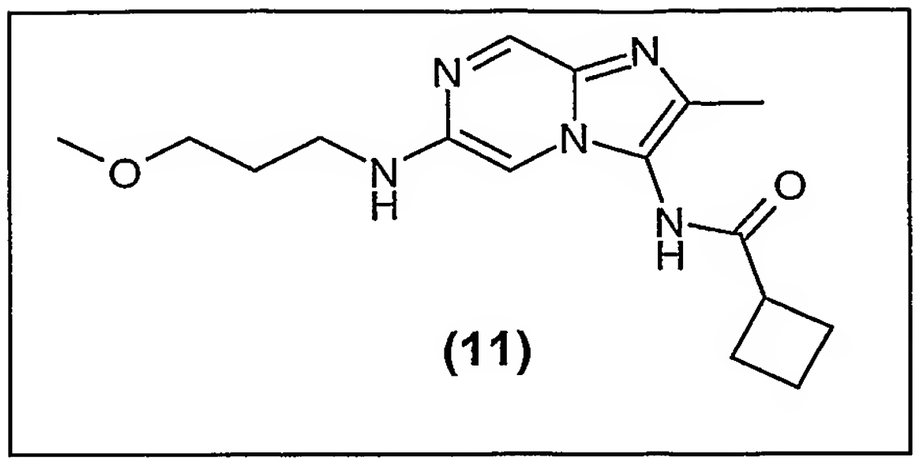
General procedure for the synthesis of compounds of formula (II).



(II)

The reactions were carried out in stem tubes with a 96 well stem shaker. Each tube was charged with a compound of formula (G) (0.3 mmol), followed by the addition of propan-2-ol (0.75 ml), a solution of the amine in propan-2-ol (0.6 mmol, 0.25 ml), a solution of 2,6-dimethylphenol in propan-2-ol (0.24 mmol, 0.25ml), potassium phosphate (0.6 mmol), and copper iodide (0.06 mmol). The reaction vessels were flushed with nitrogen then heated at 80°C for 22h. After this time the reactions were filtered then purified by preparative HPLC.

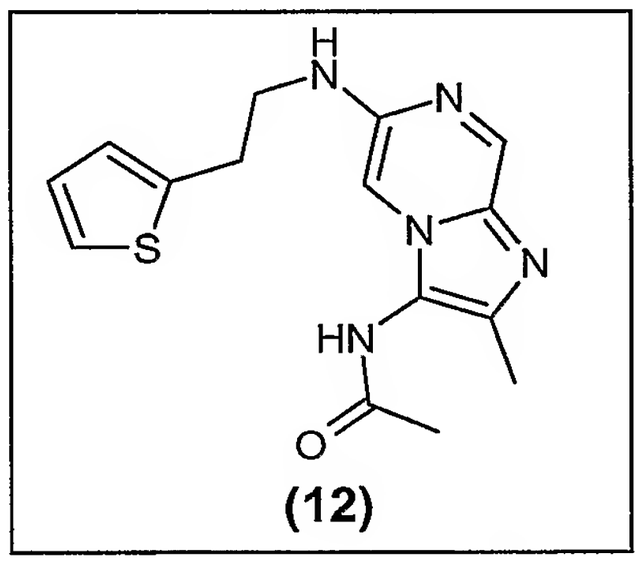
Typical example of compound of formula (II); *cyclobutanecarboxylic acid [6-(3-methyoxy-propylamino)-2-methyl-imidazo[1,2-a]pyrazin-3-yl]-amide* ***(11)***.



(11)

Yield 43.6 mg, 46%; *m/z* (ES) 318 $(M+1)^+$; HPLC 100%.

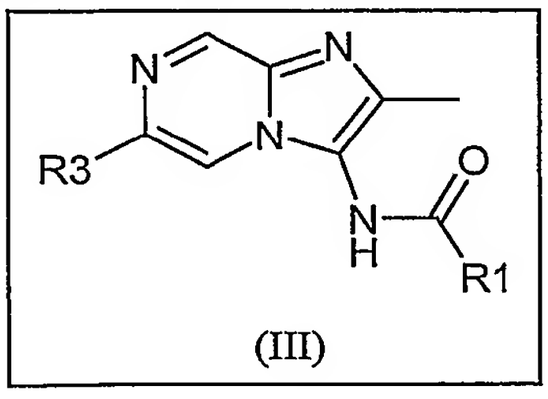
Typical example of compound of formula (II); *N-[2-methyl-6-(2-thiophen-2-yl-ethylamino)-imidazo[1,2-a]pyrazin-3-yl]-acetamide* ***(12)***.



(12)

Yield 30.2 mg, 32%; *m/z* (ES) 316 $(M+1)^+$; HPLC 100%.

General procedure for the synthesis of compounds of formula (III)

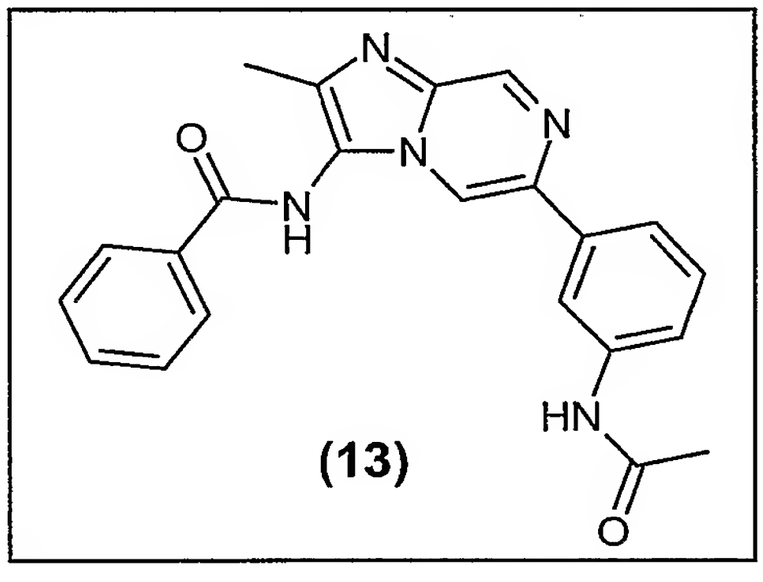


(III)

The reactions were carried out in stem tubes with a 96 well stem shaker. To a solution of a compound of formula (G) in DMF (0.3mmol, 0.5ml) was added a solution of boronic acid in DMF (0.36mmol, 0.6ml) and 1.5M

Na_2CO_3(aq.) solution (0.75mmol, 0.5ml). The reaction vessels were then placed in a nitrogen filled glovebox for 30min. Two solutions of palladium acetate (95mg) and triphenylphosphine (335mg) in 1,4-dioxane (15ml) were freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml) was added to each reaction vessel inside the glovebox. The vessels were screw capped and then heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative HPLC.

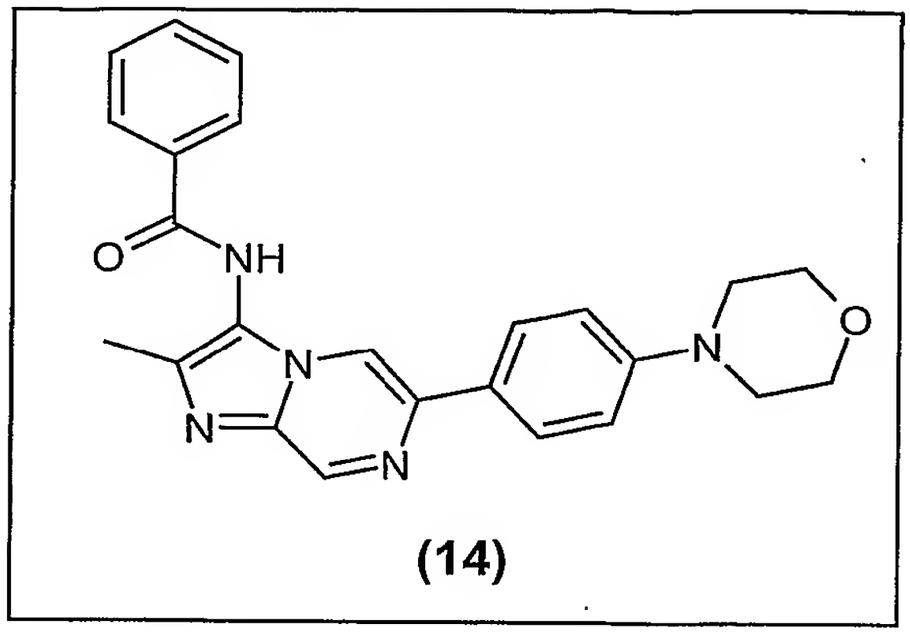
Typical example of compound of formula type (III); *N-[6-(3-acetylamino-phenyl)-2-methyl-imidazo[1,2-a]pyrazin-3-yl]-benzamide* ***(13)***.



(13)

Yield 97.0 mg, 83%; δ_H (250 MHz, DMSO) 2.04 (s, 1H), 2.37 (s, 3H), 7.36 (t, *J* 8.0, 1H), 7.56-7.72 (m, 5H), 8.09-8.12 (m, 2H), 8.22-8.23 (m, 1H), 8.58 (d, *J* 1.4, 1H), 9.06 (d, *J* 1.4, 1H), 10.07 (s, 1H), 10.62 (s, 1H); *m/z* (ES) 386 $(M+1)^+$; HPLC 98%.

Typical example of compound of formula type (III); *N-[2-methyl-6-(4-morpholin-4-yl-phenyl)-imidazo[1,2-a]pyrazin-3-yl]-benzamide* ***(14)***.



(14)

Yield 90.3 mg, 72%; δ_H (250 MHz, DMSO) 2.35 (s, 3H), 3.14-3.17 (m, 4H), 3.71-3.75 (m, 4H), 7.60 (d, *J* 8.9, 2H), 8.11 (d, *J* 8.4, 2H), 8.56 (d, *J* 1.4, 1H), 9.02 (d, *J* 1.4, 1H), 10.57 (s, 1H); *m/z* (ES) 414 $(M+1)^+$; HPLC 100%.

Purification Conditions

All compounds have a minimum purity level ≥ 80% as measured by LCMS at 254 nm.

The columns used for the preparative HPLC purification of the various scaffolds are outlined in Table 1:

Table 1

Scaffold	Column
Formula (I) and (II)	Varian Ansys MetaChem Polaris C18 10μm 21.2 x 150mm
Formula (III)	Phenomenex Luna 10μm phenyl-hexyl 21.20 x 150mm.

The gradient used for compounds of formulas (I) and (II) was 95% water (10mmol NH_3HCO_3) 5% THF/MeOH (3:1) for 1 min to 5% water (10mmol NH_3HCO_3) / 95% THF/MeOH (3:1) over 8.0 min then held at 5% water (10mmol NH_3HCO_3) / 95% THF/MeOH (3:1) for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

The gradient used for compounds of formula (III) was 95% water (0.2% TFA/10% methanol) 5% acetonitrile (10% methanol) for 1 min to 5% water (0.2% TFA/10% methanol) / 95% acetonitrile (10% methanol) over 8.0 min then held at 5% water (0.2% TFA/10% methanol) / 95% acetonitrile (10% methanol) for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

A flow rate of 25 ml/min is used for both methods.

The conditions used for the analytical HPLC analysis following preparative HPLC purification are outlined in Table 2:

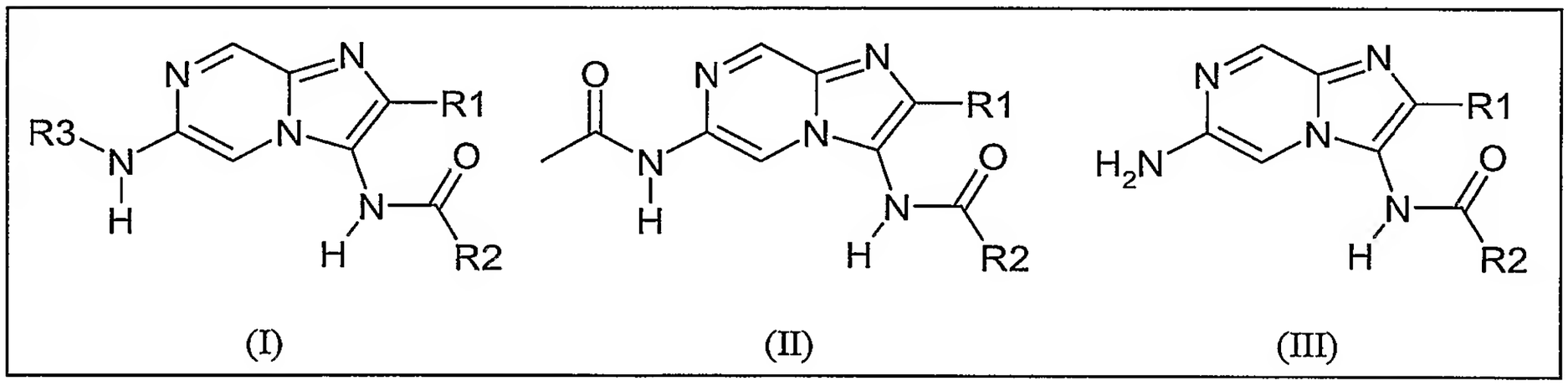
Table 2

Conditions	Detection
Column: Waters Xterra® Prep MS C18 5μm 4.6 x 100mm. **Gradient**: 95% water (10 mM NH_3HCO_3) / 5% ACN for 0.5 min then 95% water (10 mM NH_3HCO_3) / 5% ACN to 2% water (10 mM NH_3HCO_3) / 98% ACN over 3.5 min. Held at 2% water (10 mM NH_3HCO_3) / 98% ACN for 0.5 min. The solvent mixture is then returned to the initial conditions over 0.1 min and the system allowed to re-equilibrate for 0.2 min. **Flow rate:** 2.0 ml/min. **Temperature:** 30 °C. **Injection volume:** 5 μm partial loop.	UV detection at 254 nm (diode array range 210-280nm). **Electrospray ionisation**: Cone voltage: 30 V. Cone temperature: 20 °C. Source temperature 150 °C. RF lens voltage: 0.0 V. Ion energy: 0.5 eV. Multiplier: 650 V.

LIBRARY SFK11

SFK11 is designed to have primary focus on the FGF receptor-1 kinase, a member of a small group of kinases (Hanks' Group XV kinases) which are fairly typical of the receptor tyrosine kinase family, and a key anti-angiogenesis target. The library has a broader secondary focus on other members of the tyrosine kinase family. The central design of the library is based on a novel application of the imidazo[1,2-a]pyrazine scaffold. Good docking was observed for the imidazo[1,2a]pyrazine scaffold when this was substituted with 3-amino and 5-amino functions, with a characteristic double H-bond being formed between the backbone Ala^{564} of the ATP site of FGF receptor-1 and the 5, ring-6-diaza "amidine" system.

The invention provides a compound library comprising or consisting of a set of structurally related compounds of the general formula (I), (II) and (III):

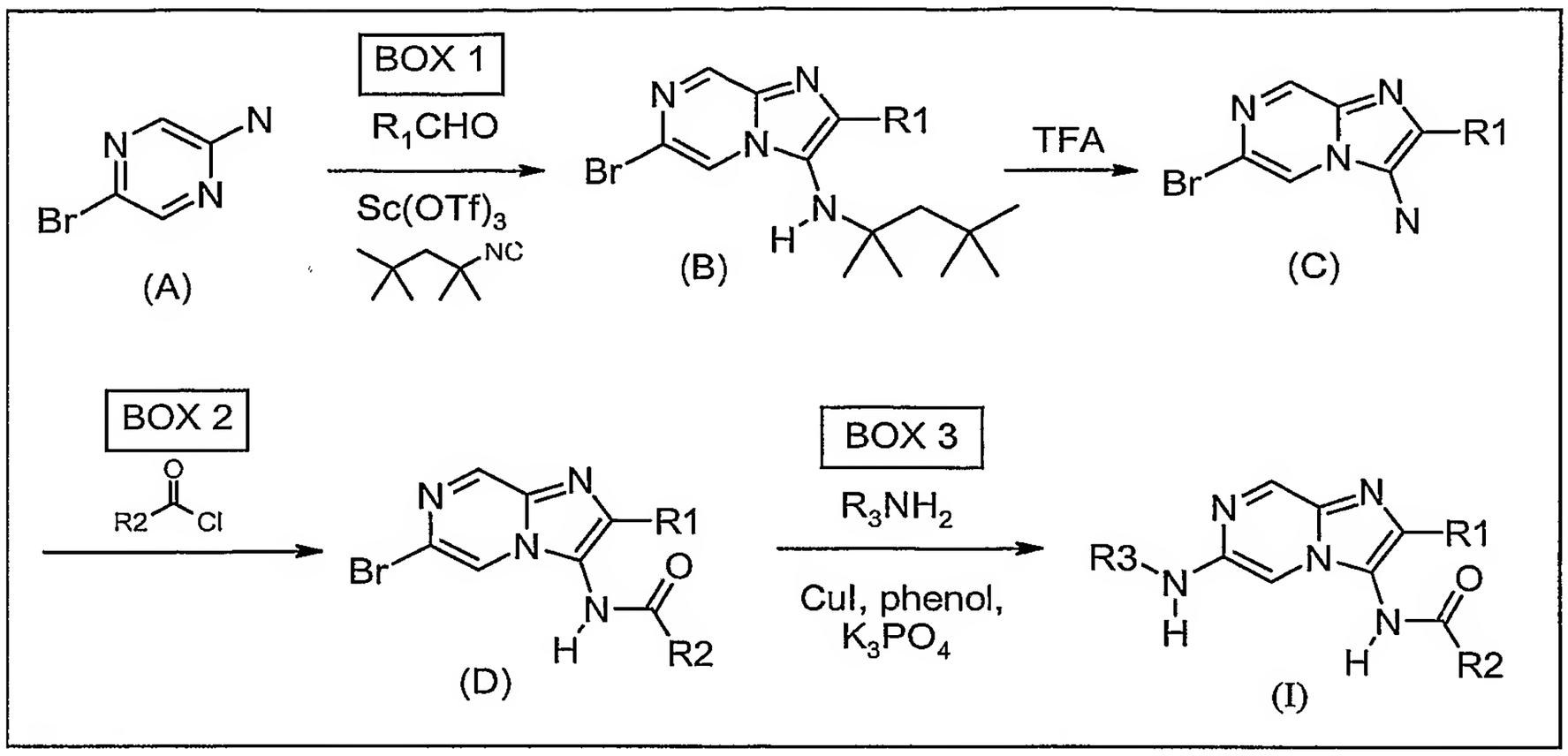


Wherein R_1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear

one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; R_2 is alkyl having from 1 to 20 carbon atoms which may be linear or branched and may contain one or more heteroatoms, alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and wherein R_3 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms or cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

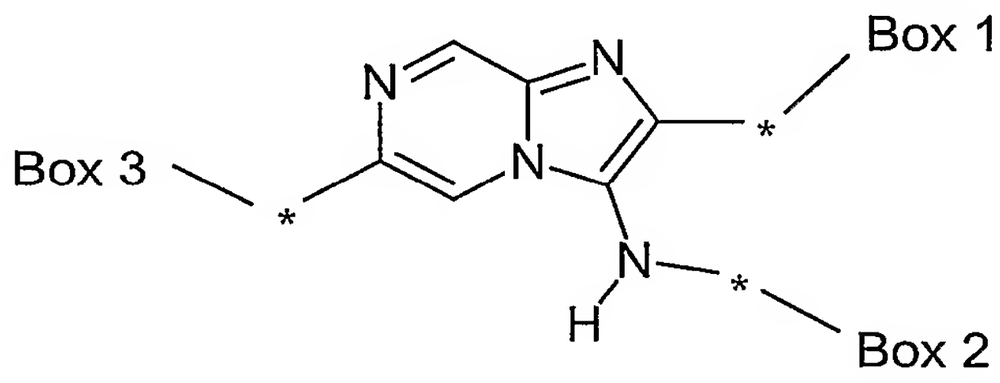
Scheme for synthesising compounds of formula (I) (PS109)

A general scheme for introducing substituents to produce compounds of SFK11 PS109, is as follows:



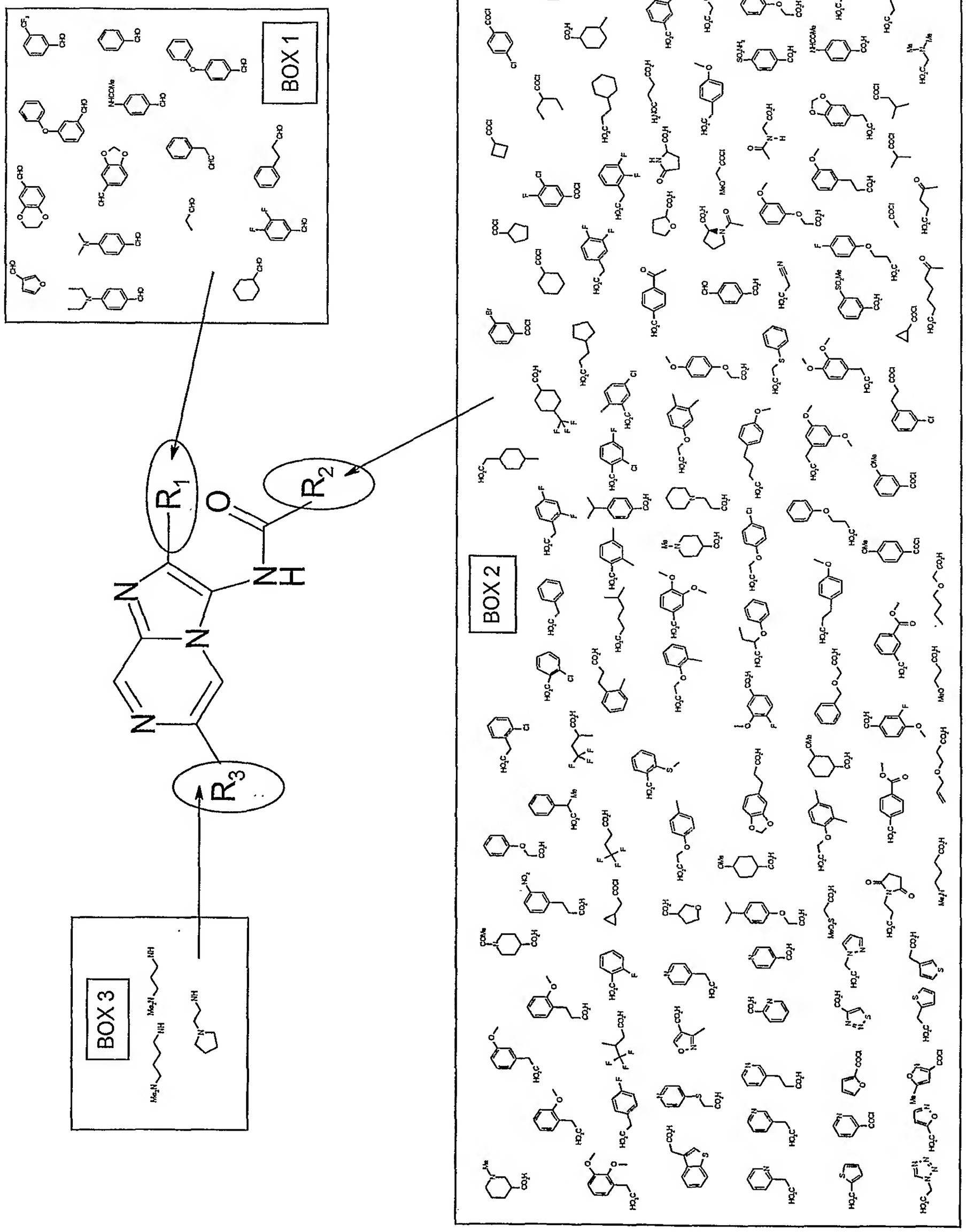
2-Amino-5-bromopyrazine (A) can be converted to the substituted 3-amino-6-bromoimidazo[1,2-a]pyrazines (B) using the aldehydes described in Box 1 and then deprotected to give primary amines (C). The resultant amines can be acylated with acid chlorides prepared from the acids described in Box 2 to give amides (D). The final compounds (I) can be prepared by reacting 6-bromoimidazo[1,2-a]pyrazines (D) with the amines described in Box 3.

The permitted substituents at positions R_1, R_2 and R_3 are shown in Boxes 1, 2 and 3 respectively, in the following schematic diagram.



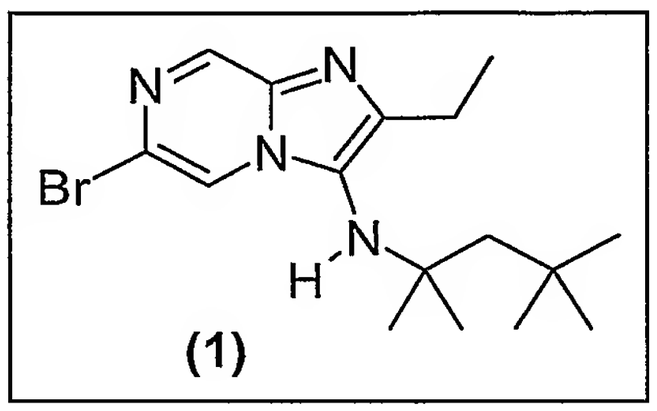
SFK11

Scatter Diagram


BOX 1
BOX 2
BOX 3
R1
R2
R3
O
NH
N
N
N

General Procedures

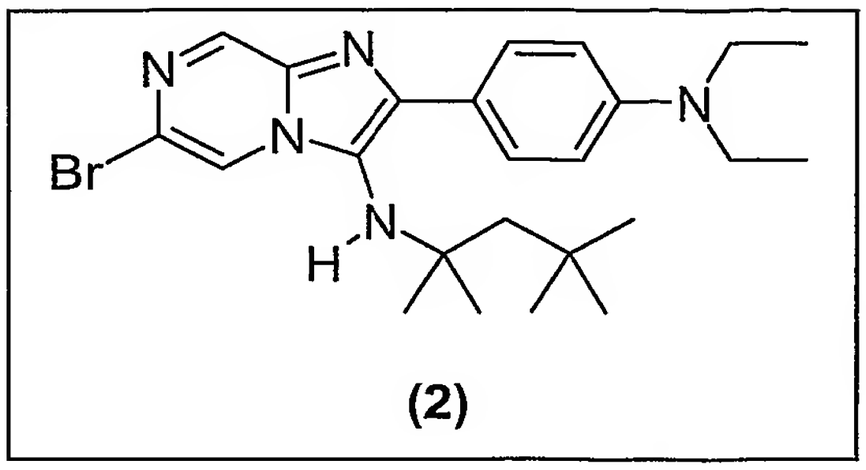
Typical example of compound of formula (B), as described in general reaction scheme; *(6-bromo-2-ethylimidazo[1,2-a]pyrazin-3-yl)-(1,1,3,3-tetramethylbutyl)-amine* ***(1)***.



(1)

To a cooled solution (0 °C) of 2-amino-5-bromopyrazine (A) (34.6 g, 200 mmol) and scandium trifluoromethanesulfonate (4.92 g, 10 mmol) in methanol (480 mL) was added propionaldehyde (145 mL, 2 mol). After allowing to warm to room temperature for 30 minutes, the solution was re-cooled to 0 °C and 1,1,3,3-tetramethylbutyl isocyanide (38.6 mL, 220 mmol) was added to the solution. After stirring for 16 hours at room temperature, the reaction mixture was acidified to pH 1 using hydrochloric acid (1M). The methanol was removed *in vacuo* and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was separated, dried and concentrated to yield a brown oil, which was purified by column chromatography (25% ethyl acetate/hexane) to yield the desired imidazo[1,2-a]pyrazine **(1)** as a pale yellow oil (29.7 g, 42%). HPLC 98%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.68 (d, J = 0.7 Hz, 1H), 8.22 (d, J = 0.7 Hz, 1H), 2.89 (brs, 1H), 2.81 (q, J = 7.5 Hz, 2H), 1.69 (s, 2H), 1.38 (t, J = 7.5 Hz, 3H), 1.19 (s, 6H), 1.12 (s, 9H); MS (APCI) 355/353 $[M+H]^+$.

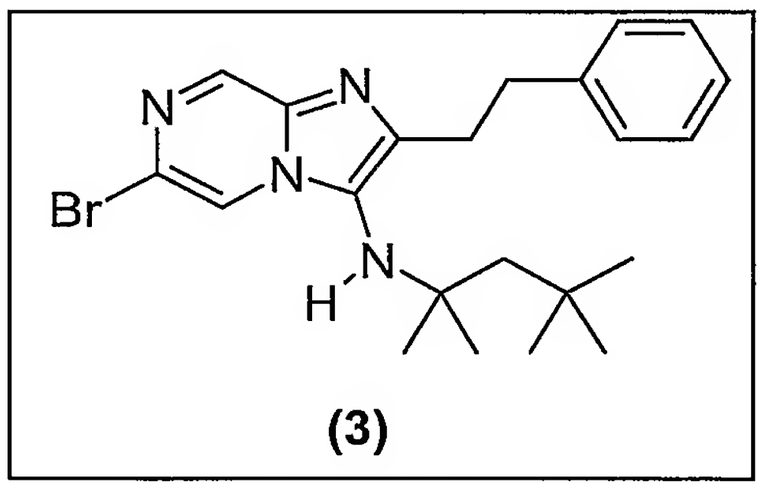
Typical example of compound of formula (B), as described in general reaction scheme; *[6-bromo-2-(4-diethylaminophenyl)-imidazo[1,2-a]pyrazin-3-yl]-(1,1,3,3-tetramethylbutyl)-amine* ***(2)***.



(2)

Yield 2.48 g, 58%; HPLC 99%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.69 (d, *J* = 1.2 Hz, 1H), 8.23 (d, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 3.37 (q, *J* = 7.0 Hz, 4H), (q, *J* = 7.0 Hz, 4H), 1.61 (s, 2H), 1.20 (t, *J* = 7.0 Hz, 6H), 1.06 (s, 9H), 1.01 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 147.8,145.0, 141.1, 136.3, 129.4, 124.4, 122.3, 120.3, 116.6, 111.3, 61.4, 57.0, 44.6, 31.8, 31.7, 29.1, 12.6; MS (APCI) 474/472 $[M+H]^+$.

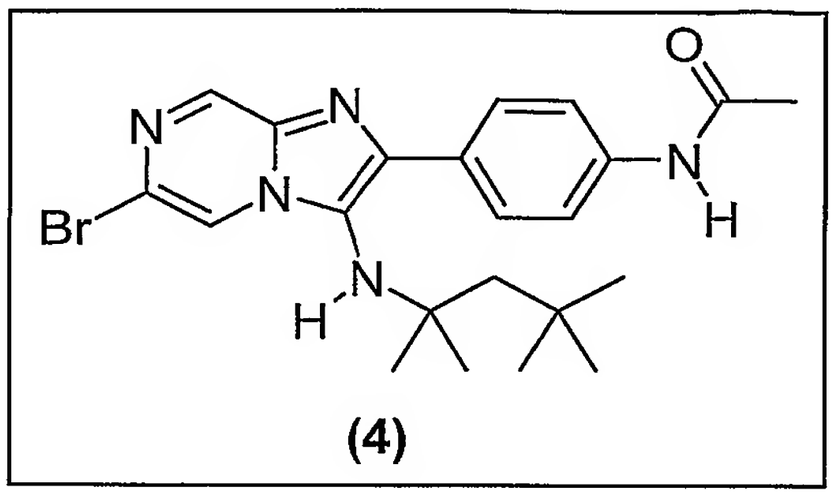
Typical example of compound of formula (B), as described in general reaction scheme; *(6-bromo-2-phenethylimidazo[1,2-a]pyrazin-3-yl)-(1,1,3,3-tetramethylbutyl)-amine* ***(3)***.



(3)

Yield 29.7g, 33%; HPLC 91%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.70 (d, *J* = 1.2 Hz, 1H), 8.15 (d, *J* = 1.2 Hz, 1H), 7.23 (m, 3H), 7.10 (m, 2H), 3.09 (m, 4H), 1.54 (s, 2H), 1.09 (s, 6H), 1.05 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 145.4, 141.4, 141.2, 136.5, 128.5, 128.4, 126.3, 126.1, 122.4, 116.8, 60.1, 56.6, 35.5, 31.8, 31.5, 30.4, 29.2; MS (APCI) 431/429 $[M+H]^+$.

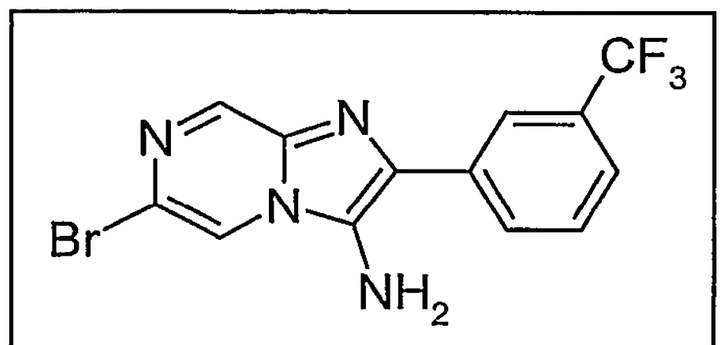
Typical example of compound of formula (B), as described in general reaction scheme; *N-{4-[6-bromo-3-(1,1,3,3-tetramethylbutylamino)-imidazo[1,2-a]pyrazin-2-yl]-phenyl}-acetamide* ***(4)***.



(4)

Yield 43.0g, 47%; HPLC 98%; ^{1}H NMR (250 MHz, DMSO) δ 10.04 (s, 1H), 8.75 (d, *J* = 1.2 Hz, 1H), 8.64 (d, *J* = 1.2 Hz, 1H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 4.60 (s, 1H), 2.05 (s, 3H), 1.60 (s, 2H), 0.97 (s, 9H), 0.90 (s, 6H); ^{13}C NMR (62.9 MHz, DMSO) δ 168.3, 142.2, 141.5, 139.2, 135.7, 128.7, 128.5, 125.8, 121.6, 118.3, 117.3, 60.8, 55.5, 31.5, 31.3, 28.7, 24.0; MS (APCI) 460/458 $[M+H]^{+}$.

Typical example of compound of formula (C), as described in general reaction scheme; *6-bromo-2-(3-trifluoromethylphenyl)-imidazo[1,2-a]pyrazin-3-ylamine* ***(5)***.

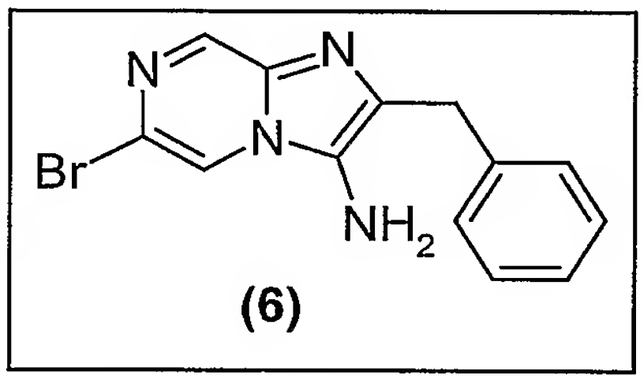


(5)

Imidazo[1,2-a]pyrazine (4.82 g, 12 mmol) was dissolved in a solution of trifluoroacetic acid (12 mL) and dichloromethane (12 mL). After stirring at room temperature for 1 hour the reaction was judged by HPLC analysis to

have reached completion. The dark solution was concentrated and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was separated, dried and concentrated to yield the desired amine **(5)** as an orange solid (11.1g, 92%). HPLC 96%; ^{1}H NMR (250 MHz, DMSO) δ 8.68 (d, *J* = 1.2 Hz, 1H), 8.63 (d, *J* = 1.2 Hz, 1H), 8.29 (m, 2H), 7.69 (m, 1H), 7.66 (m, 1H), 6.18 (s, 2H); MS (APCI) 359/357 $[M+H]^+$.

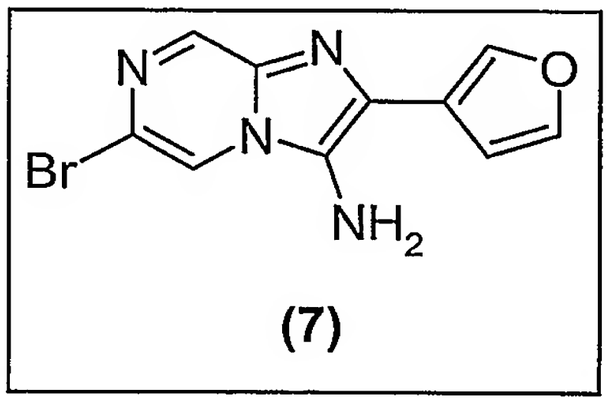
Typical example of compound of formula (C), as described in general reaction scheme; *2-benzyl-6-bromoimidazo[1,2-a]pyrazin-3-ylamine* ***(6)***.



(6)

Yield 1.12g, 90%; HPLC 90%; ^{1}H NMR (250 MHz, DMSO) δ 8.47 (s, 1H), 8.32 (s, 1H), 7.26 (m, 5H), 5.86 (s, 2H), 4.07 (s, 2H); ^{13}C NMR (62.9 MHz, DMSO) δ 139.8, 139.7, 132.7, 132.3, 130.2, 128.6, 128.1, 125.9, 121.4, 114.1, 32.3; MS (APCI) 305/303 $[M+H]^+$.

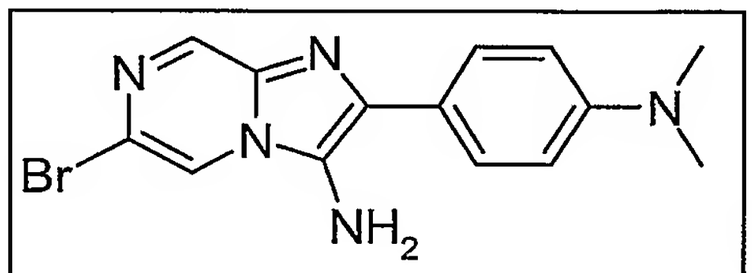
Typical example of compound of formula (C), as described in general reaction scheme; *6-bromo-2-furan-3-ylimidazo[1,2-a]pyrazin-3-ylamine* ***(7)***.



(7)

Yield 13.2g, 91%; HPLC 92%; ^{1}H NMR (250 MHz, DMSO) δ 8.56 (d, *J* = 1.2 Hz, 1H), 8.49 (d, *J* = 1.2 Hz, 1H), 8.28 (s, 1H), 7.78 (s, 1H), 7.01 (s, 1H), 5.95 (s, 2H); ^{13}C NMR (62.9 MHz, DMSO) δ 142.3, 138.9, 138.5, 131.7, 127.6, 123.1, 120.1, 118.1, 113.0, 107.6; MS (APCI) 281/279 $[M+H]^{+}$.

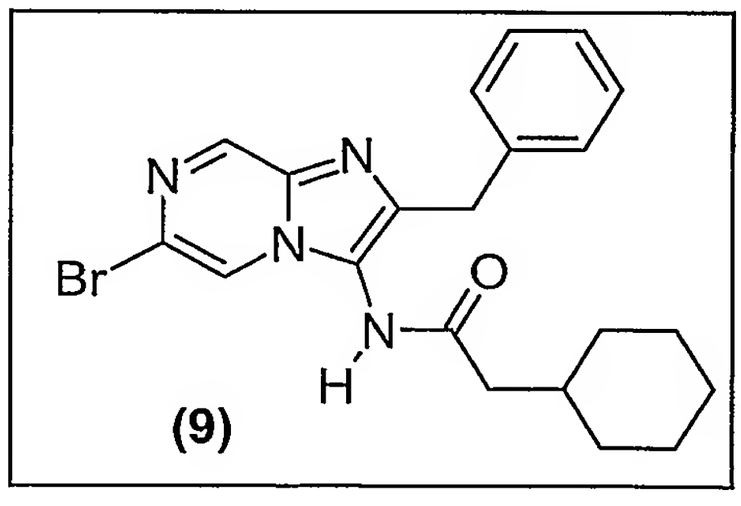
Typical example of compound of formula (C), as described in general reaction scheme; *6-bromo-2-(4-dimethylaminophenyl)imidazo[1,2-a]pyrazin-3-ylamine* ***(8)***.



(8)

Yield 16.5 g, 90%; HPLC 80%; ^{1}H NMR (250 MHz, DMSO) δ 8.53 (d, *J* = 1.2 Hz, 1H), 8.48 (d, *J* = 1.2 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 5.85 (s, 2H), 2.93 (s, 6H); ^{13}C NMR (62.9 MHz, DMSO) δ 149.6, 139.5, 133.0, 128.3, 127.5, 121.5, 121.3, 114.0, 112.1, 39.9; MS (APCI) 334/332 $[M+H]^{+}$.

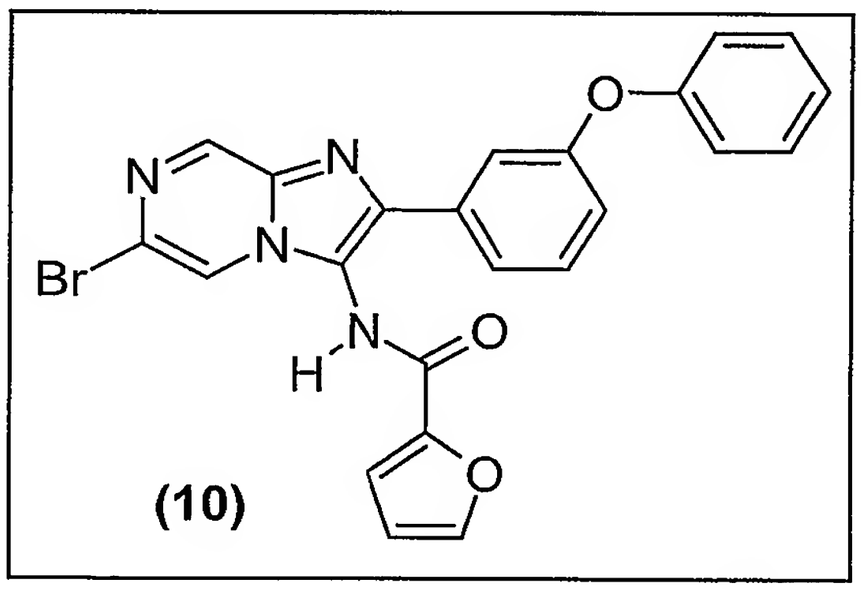
Typical example of compound of formula (D), as described in general reaction scheme; *N-(2-benzyl-6-bromoimidazo[1,2-a]pyrazin-3-yl)-2-cyclohexylacetamide* ***(9)***.



(9)

To a solution of cyclohexylacetic acid (57 mg, 0.4 mmol) in THF (0.5 mL) was added oxalyl chloride (70 μL, 0.8 mmol). After stirring for 2 hours, 2-benzyl-6-bromoimidazo[1,2-a]pyrazin-3-ylamine **(6)** (91mg, 0.3mmol) and a solution of diisopropylethylamine (0.14 mL, 0.8 mmol) in THF was added to the reaction mixture which was heated to 60 °C for 16 hours. The resultant suspension was diluted with dimethylsulfoxide (1 mL), filtered and purified by reverse-phase preparative HPLC to yield the desired product **(9)** (9.4mg, 7%). HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.18 (s, 1H), 8.80 (d, *J* = 1.2 Hz, 1H), 8.33 (d, *J* = 1.2 Hz, 1H), 7.21 (m, 5H), 4.01 (s, 2H), 2.32 (d, *J* = 6.9 Hz, 2H), 1.71 (m, 6H), 1.29-0.90 (m, 5H); MS (ES) 429/427 $[M+H]^+$.

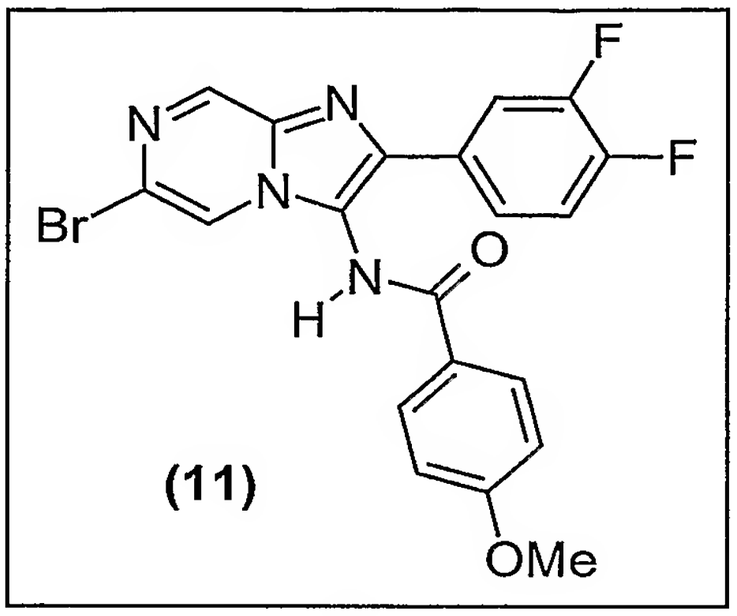
Typical example of compound of formula (D), as described in general reaction scheme; *furoic acid [6-bromo-2-(3-phenoxyphenyl)imidazo[1,2-a]pyrazin-3-yl]-amide* ***(10)***.



(10)

Yield 89.8 mg, 63%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.77 (s, 1H), 8.98 (d, *J* = 1.3 Hz, 1H), 8.77 (d, *J* = 1.3 Hz, 1H), 8.02 (dd, *J* = 0.7, 1.7 Hz, 1H), 7.73 (dt, *J* = 1.2, 8.1 Hz, 1H), 7.55 (dd, *J* = 1.6, 2.4 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.32 (m, 3H), 7.04 (m, 4H), 6.76 (dd, *J* = 1.7, 3.5 Hz, 1H); MS (ES) 477/475 $[M+H]^+$.

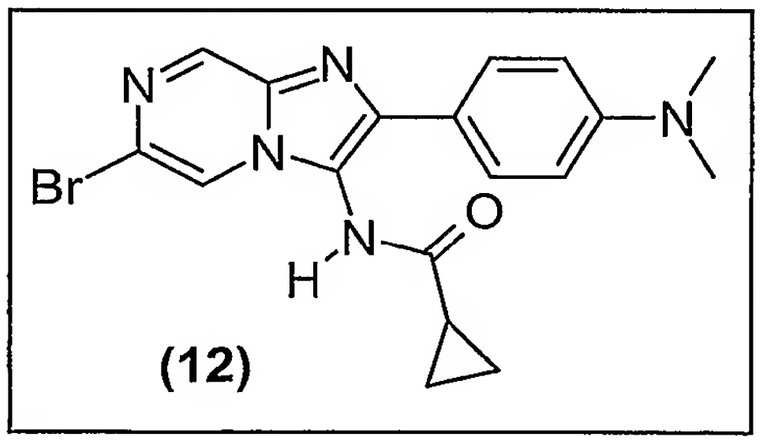
Typical example of compound of formula (D), as described in general reaction scheme; *N-[6-bromo-2-(3,4-difluorophenyl)imidazo[1,2-a]pyrazin-3-yl]-4-methoxy benzamide* ***(11)***.



(11)

Yield 23.4 mg, 17%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.74 (s, 1H), 9.01 (d, *J* = 1.3 Hz, 1H), 8.77 (d, *J* = 1.3 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.95 (m, 1H), 7.81 (m, 1H), 7.56 (m, 1H), 7.13 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H); MS (ES) 461/459 $[M+H]^+$.

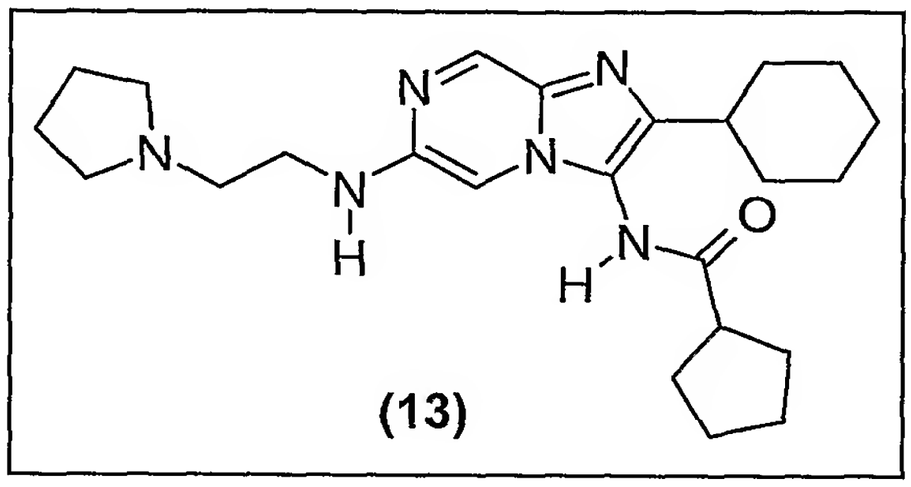
Typical example of compound of formula (D), as described in general reaction scheme; *cyclopropanecarboxylic acid [6-bromo-2-(4-dimethylaminophenyl)imidazo [1,2-a]pyrazin-3-yl]-amide* ***(12)***.



(12)

Yield 3.7 mg, 3%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.59 (s, 1H), 8.84 (d, *J* = 1.3 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 2.96 (s, 6H), 1.96 (m, 1H), 0.93 (m, 4H); MS (ES) 402/400 $[M+H]^+$.

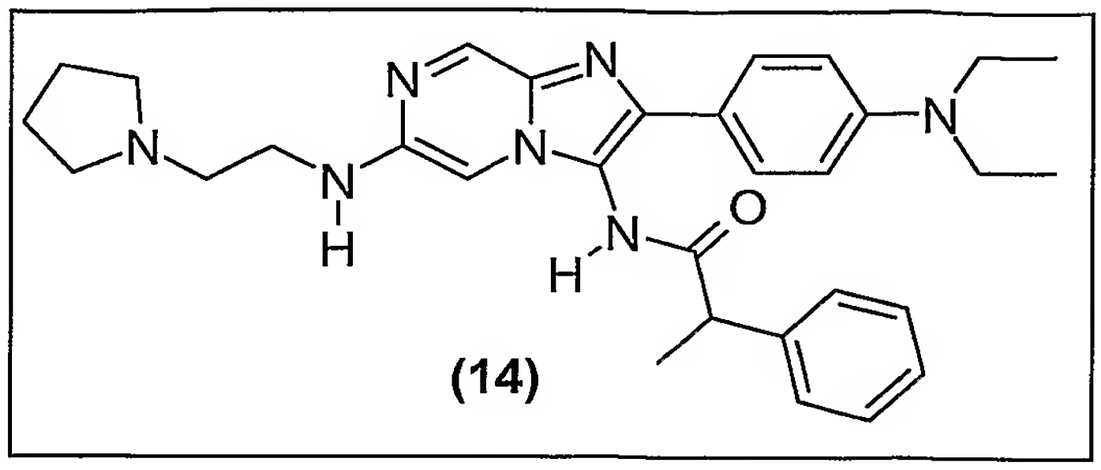
Typical example of compound of formula (I), as described in general reaction scheme; *cyclopentanecarboxylic acid [2-cyclohexyl-6-(2-pyrrolidin-1-yl-ethylamino)-imidazo[1,2-a]pyrazin-3-yl]-amide* ***(13)***.



(13)

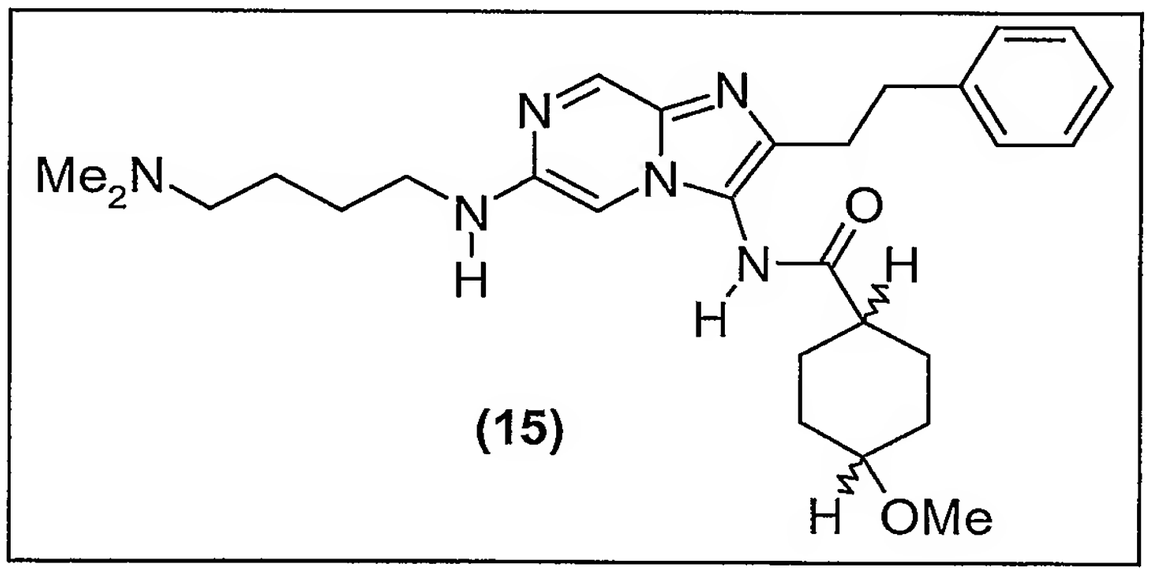
To a 'Stem' reaction tube was added sequentially cyclopentanecarboxylic acid (6-bromo-2-cyclohexylimidazo[1,2-a]pyrazin-3-yl)-amide (91.2 mg, 0.23 mmol), potassium phosphate (0.13 g, 0.6 mmol), a solution of 2,6-dimethylphenol (0.29 mg, 0.24 mmol) in isopropanol (0.25 mL), a solution of *N*-(2-aminoethyl)pyrrolidine (69 mg, 0.6 mmol) in isopropanol (0.25 mL), isopropanol (0.25 mL) and copper (I) iodide (11 mg, 0.06 mmol). The reaction tubes were flushed with nitrogen, sealed and heated at 80 °C for 16 hours. After allowing to cool, the reaction mixture was diluted with DMSO (1 mL), filtered and purified by reverse-phase preparative HPLC to yield the desired product **(13)** as a dark solid (41.2 mg, 42%). HPLC 100%; MS (ES) 425 $[M+H]^+$.

Typical example of compound of formula (I), as described in general reaction scheme; *N-[2-(4-diethylaminophenyl)-6-(2-pyrrolidin-1-yl-ethylamino)-imidazo[1,2-a]pyrazin-3-yl]-2-phenylpropionamide* ***(14)***.



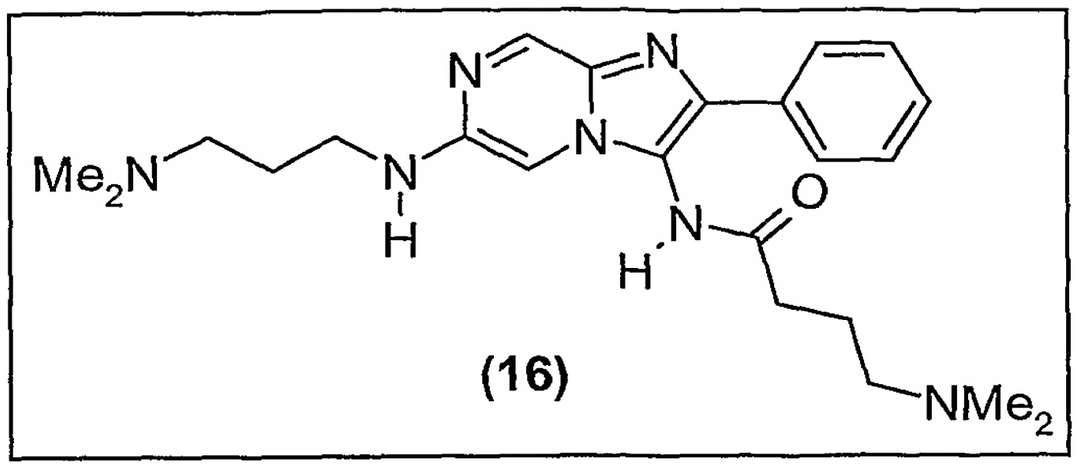
Yield 38.5 mg, 32%; HPLC 100%; MS (ES) 526 $[M+H]^+$.

Typical example of compound of formula (I), as described in general reaction scheme; *4-methoxycyclohexanecarboxylic acid [6-(4-dimethylaminobutylamino)-2-phenethylimidazo[1,2-a]pyrazin-3-yl]-amide* ***(15)***.



Yield 16.8 mg, 36%; HPLC 100%; MS (ES) 421 $[M+H]^+$.

Typical example of compound of formula (I), as described in general reaction scheme; *4-dimethylamino-N-[6-(3-dimethylaminopropylamino)-2-phenylimidazo [1,2-a]pyrazin-3-yl]-butyramide* ***(16)***.

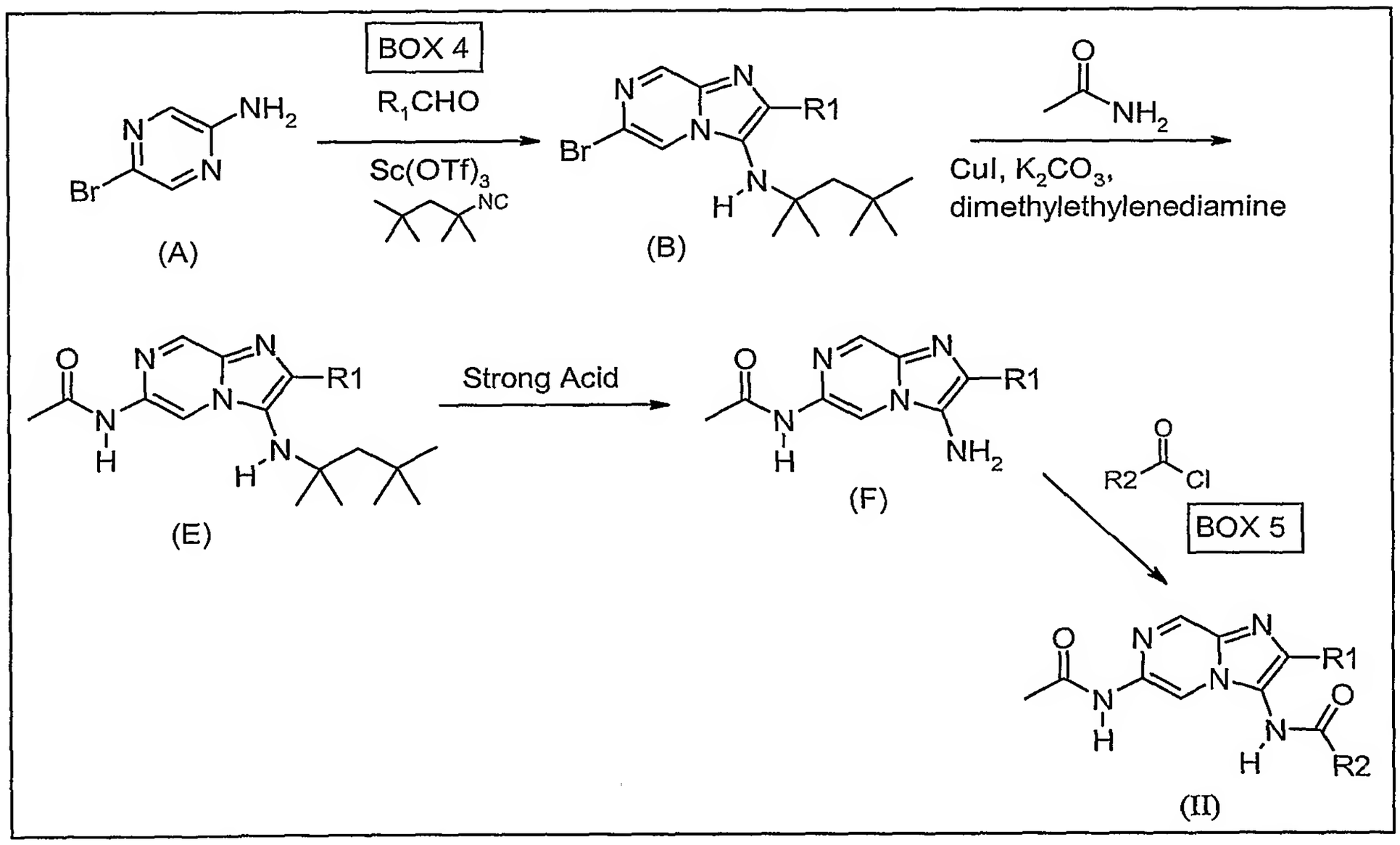


(16)

Yield 18.0 mg, 17%; HPLC 100%; MS (ES) 424 $[M+H]^+$.

Scheme for synthesising compounds of formula (II) (PS109)

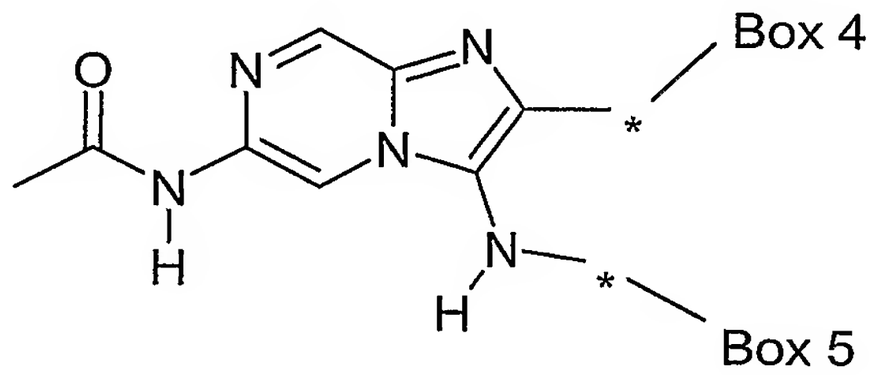
A general scheme for introducing substituents to produce compounds of SFK11 PS109, is as follows:



2-Amino-5-bromopyrazine (A) can be converted to the substituted 3-amino-6-bromoimidazo[1,2-a]pyrazines (B) using the aldehydes described in Box 4. The intermediates (B) can then be reacted with acetamide to give amides (E). These can be deprotected to give primary amines (F).

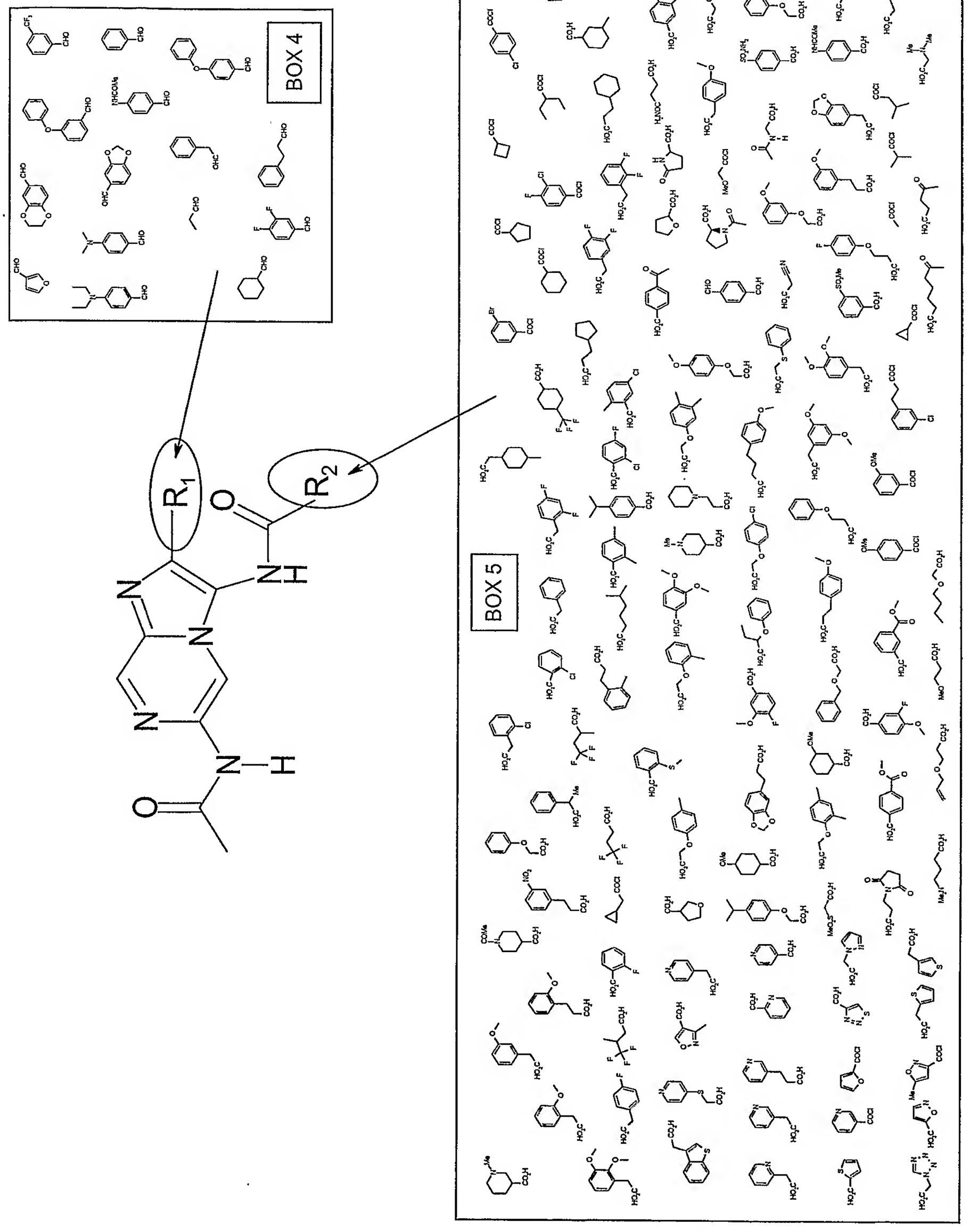
The resultant amines can be acylated with the acid chlorides prepared from the acids described in Box 5 to give the amides (II).

The permitted substituents at positions R_1 and R_2 are shown in Boxes 4 and 5 respectively, in the following schematic diagram.



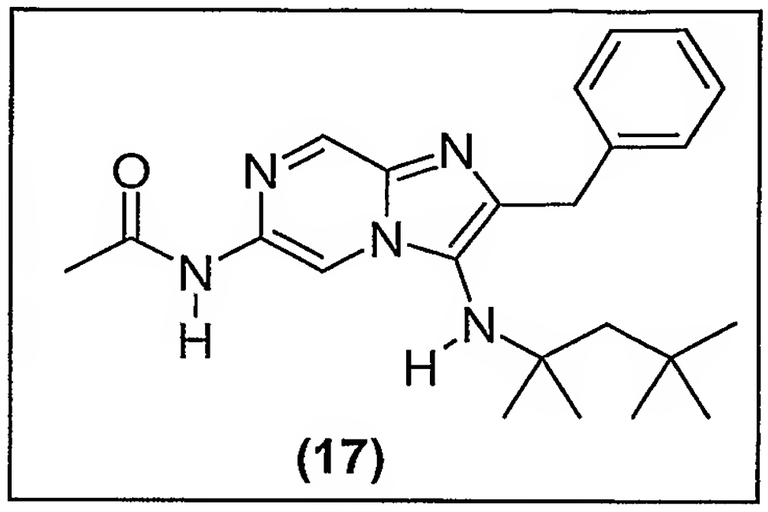
SFK11

Scatter Diagram


BOX 4
BOX 5
R1
R2
O
NH
N
N
N
N
H
O

General Procedures

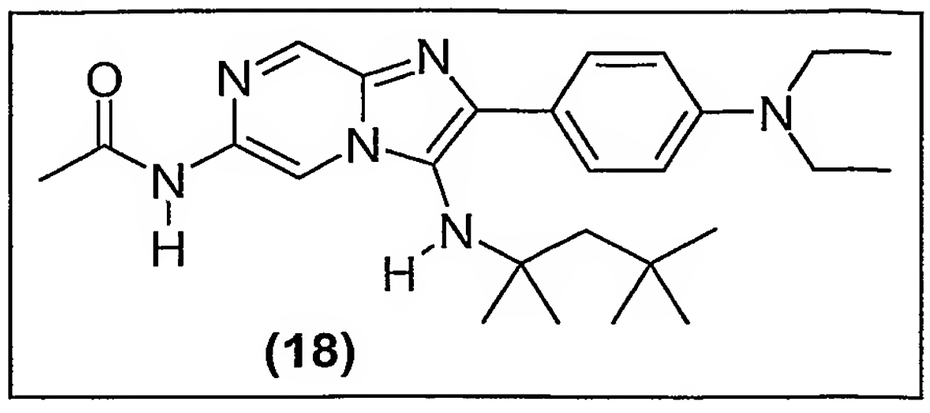
Typical example of compound of formula (E), as described in general reaction scheme; *N-[2-benzyl-3-(1,1,3,3-tetramethylbutylamino)imidazo[1,2-a]pyrazin-6-yl]-acetamide* ***(17)***.



(17)

(2-Benzyl-6-bromoimidazo[1,2-a]pyrazin-3-yl)-(1,1,3,3-tetramethylbutyl)amine (20.0 g, 48 mmol), acetamide (4.23 g, 72 mmol), copper (I) iodide (1.38 g, 7.2 mmol), *N,N'*-dimethylethylenediamine (0.77 mL, 7.2 mmol), copper bronze (0.10 g, 1.6 mmol) and potassium carbonate (13.2 g, 96 mmol) were weighed into a 250 mL round-bottom flask. After the flask was evacuated and flushed with nitrogen (× 3), toluene (54 mL) was added and the reaction mixture heated (100 °C) for 24 hours. After LCMS analysis showed that all the starting material had been consumed, the reaction mixture was diluted with ethyl acetate and filtered through a short plug of silica. The filtrate was concentrated and the residue purified by column chromatography to yield the desired amide **(17)** as a yellow solid (8.89 g, 47%). HPLC 98%; ^{1}H NMR (250 MHz, DMSO) δ 10.52 (s, 1H), 9.17 (s, 1H), 8.62 (s, 1H), 7.20 (m, 5H), 4.46 (s, 1H), 4.09 (s, 2H), 2.09 (s, 3H), 1.63 (s, 2H), 1.08 (s, 6H), 1.03 (s, 9H); MS (APCI) 394 $[M+H]^+$.

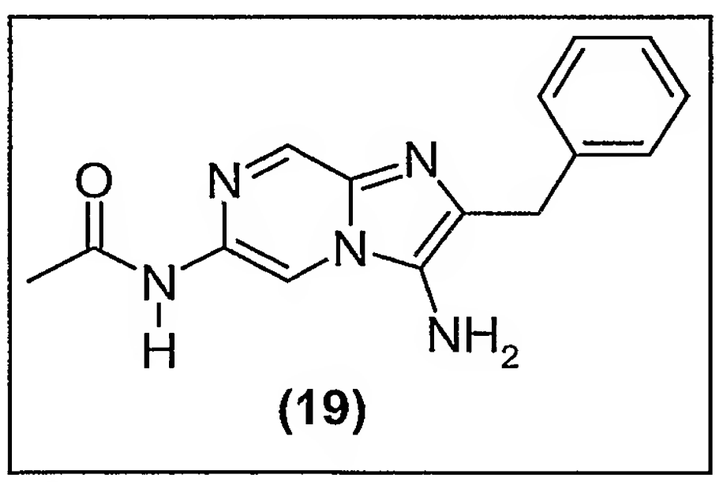
Typical example of compound of formula (E), as described in general reaction scheme; *N-[2-(4-diethylaminophenyl)-3-(1,1,3,3-tetramethylbutylamino)-imidazo[1,2-a]pyrazin-6-yl]-acetamide* ***(18)***.



(18)

Yield 5.0 g, 41%; HPLC 95%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.20 (d, *J* = 1.2 Hz, 1H), 8.75 (s, 1H), 8.66 (d, *J* = 1.2 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 4H), 3.19 (s, 1H), 2.23 (s, 3H), 1.66 (s, 2H), 1.20 (t, *J* = 7.1 Hz, 6H), 1.09 (s, 9H), 1.06 (s, 6H); MS (APCI) 451 $[M+H]^+$.

Typical example of compound of formula (F), as described in general reaction scheme; *N-(3-amino-2-benzylimidazo[1,2-a]pyrazin-6-yl)-acetamide* ***(19)***.

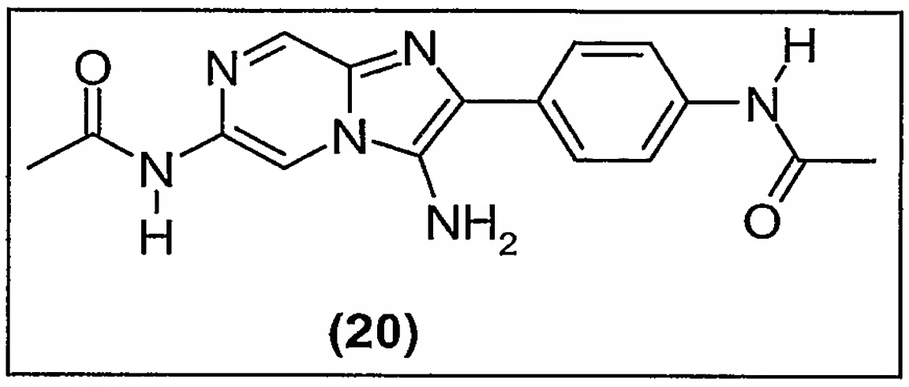


(19)

The protected amine **(17)** (5.0 g, 12.7 mmol) was weighed into a 100 mL round-bottom flask and was dissolved in 4M HCl/dioxane (30 mL). After stirring at room temperature for 16 hours, the solution was analysed by LCMS and determined to have reached completion. The reaction mixture was concentrated and the crude residue was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was separated, dried and concentrated to give the desired amine (19) as a dark yellow solid (2.1 g, 59%). HPLC 99%; ^{1}H NMR (250 MHz, DMSO) δ

10.31 (s, 1H), 8.69 (s, 1H), 8.49 (s, 1H), 7.25 (m, 5H), 5.45 (s, 2H), 4.04 (s, 2H), 2.08 (s, 3H); MS (APCI) 282 $[M+H]^+$.

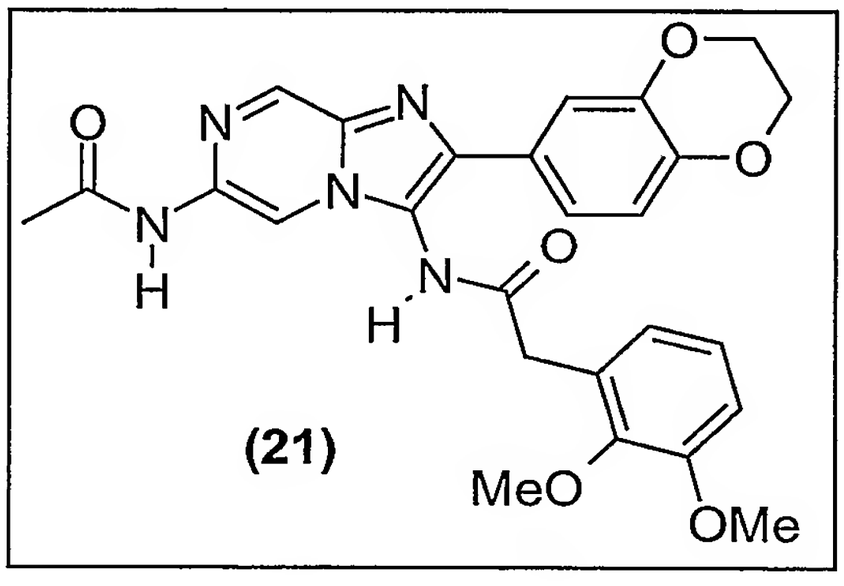
Typical example of compound of formula (F), as described in general reaction scheme; *N-[2-(4-acetylaminophenyl)-3-aminoimidazo[1,2-a]pyrazin-6-yl]-acetamide* ***(20)***.



(20)

Yield 1.37 g, 82%; HPLC 93%; ^{1}H NMR (250 MHz, DMSO) δ 10.06 (s, 1H), 8.83 (d, J = 1.2 Hz, 1H), 8.62 (d, J = 1.2 Hz, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 5.57 (s, 2H), 2.10 (s, 3H), 2.05 (s, 3H); MS (APCI) 323 $[M+H]^+$.

Typical example of compound of formula (II), as described in general reaction scheme; *N-[6-acetamido-2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-imidazo[1,2-a]pyrazin-3-yl]-2-(2,3-dimethoxyphenyl)-acetamide* ***(21)***.

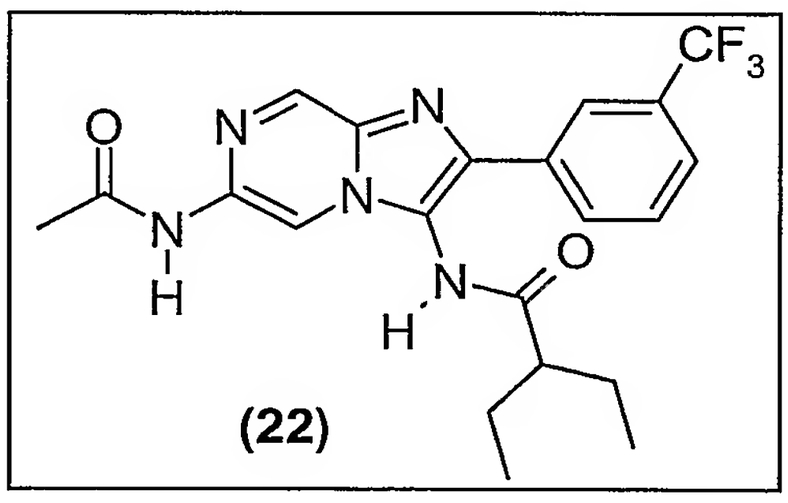


(21)

To a 'Stem' reaction tube containing 2,3-dimethoxyphenylacetic acid (58.9 mg, 0.3 mmol) in THF (0.5 mL) was added oxalyl chloride (25 μL, 0.3

mmol) and a drop of DMF. The reaction mixture was flushed with nitrogen, capped and shaken for 2 hours. Solid *N*-[3-amino-2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-imidazo[1,2-a]pyrazin-6-yl]-acetamide (65 mg, 0.2 mmol) and a solution of diisopropylethylamine (70 μL, 0.4 mmol) in THF (0.5 mL) was added to the acid chloride solution and the reaction again flushed with nitrogen and capped. After heating to 60°C for 16 hours, the reaction mixture was allowed to cool, diluted with DMSO (1mL), filtered and purified by reverse-phase preparative HPLC to yield the desired amide **(21)** as a pale yellow solid (18.2 mg, 18%); HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.62 (s, 1H), 10.46 (s, 1H), 8.90 (d, *J* = 1.4 Hz, 1H), 8.72 (d, *J* = 1.4 Hz, 1H), 7.48 (m, 1H), 6.98 (m, 5H), 4.28 (s, 4H), 3.82 (s, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 2.11 (s, 3H); MS (ES) 504 $[M+H]^+$.

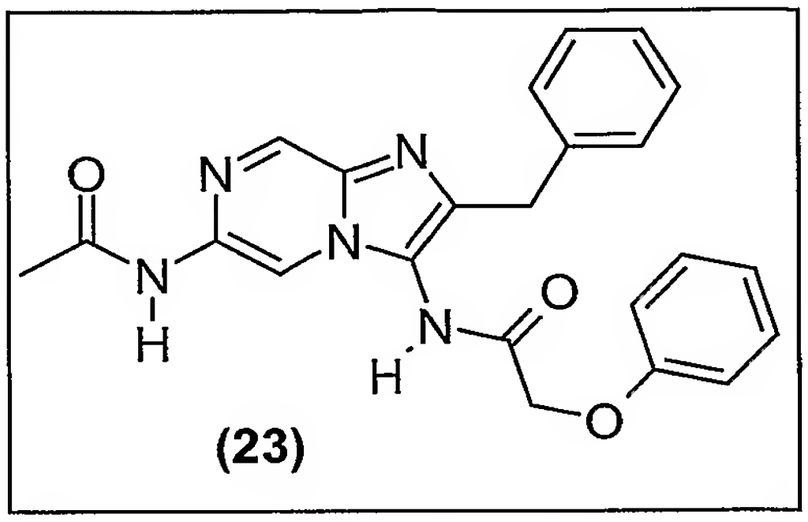
Typical example of compound of formula (II), as described in general reaction scheme; *N-[6-acetylamino-2-(3-trifluoromethylphenyl)-imidazo[1,2-a]pyrazin-3-yl]-2-ethylbutyramide* ***(22)***.



(22)

Yield 2.3 mg, 3%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.74 (s, 1H), 10.71 (s, 1H), 8.99 (d, *J* = 1.4 Hz, 1H), 8.73 (d, *J* = 1.4 Hz, 1H), 8.23 (m, 2H), 7.76 (m, 2H), 2.12 (s, 3H), 2.03 (m, 1H), 0.96 (m, 4H), 0.88 (m, 6H); MS (ES) 434 $[M+H]^+$.

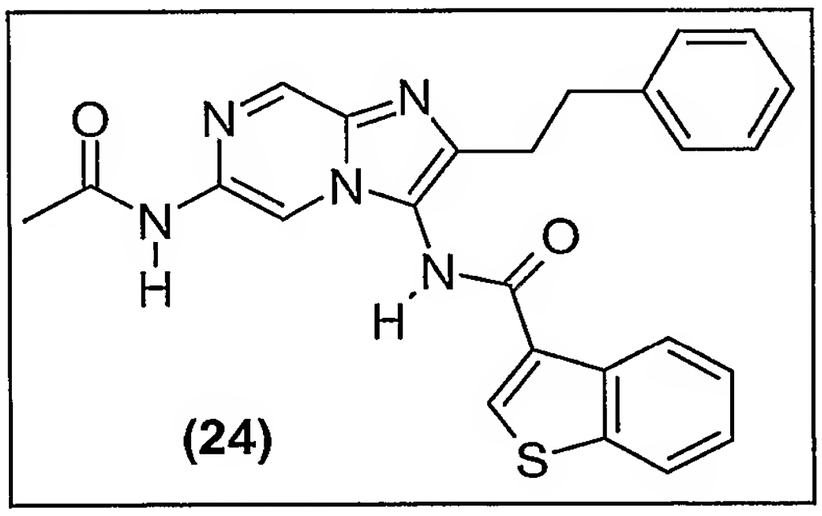
Typical example of compound of formula (II), as described in general reaction scheme; *N-(6-acetylamino-2-benzylimidazo[1,2-a]pyrazin-3-yl)-2-phenoxyacetamide* ***(23)***.



(23)

Yield 38.2 mg, 46%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.60 (s, 1H), 10.39 (s, 1H), 8.81 (d, *J* = 1.4 Hz, 1H), 8.73 (d, *J* = 1.4 Hz, 1H), 7.21 (m, 5H), 4.88 (s, 2H), 3.98 (s, 1H), 3.96 (s, 1H), 2.11 (s, 3H); MS (ES) 416 $[M+H]^+$.

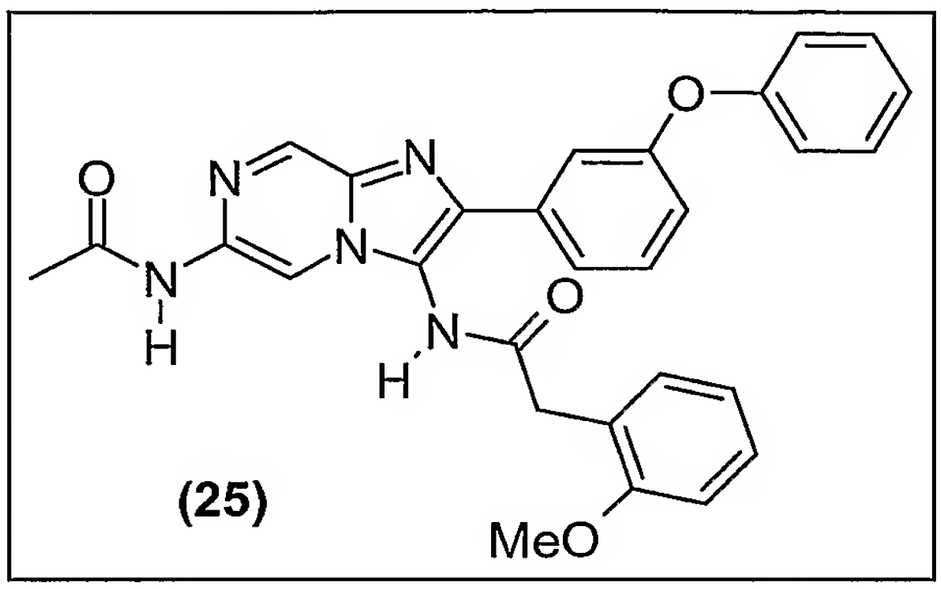
Typical example of compound of formula (II), as described in general reaction scheme; *benzo[b]thiophene-3-carboxylic acid (6-acetylamino-2-phenethylimidazo [1,2-a]pyrazin-3-yl)-amide* ***(24)***.



(24)

Yield 21.4 mg, 23%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.60 (s, 1H), 10.42 (s, 1H), 8.81 (d, *J* = 1.4 Hz, 1H), 8.80 (d, *J* = 1.4 Hz, 1H), 7.97 (m, 2H), 7.67 (s, 1H), 7.38 (m, 2H), 7.19 (m, 5H), 4.09 (s, 2H), 2.34 (s, 4H), 2.12 (s, 3H); MS (ES) 470 $[M+H]^+$.

Typical example of compound of formula (II), as described in general reaction scheme; *N-[6-acetylamino-2-(3-phenoxyphenyl)-imidazo[1,2-a]pyrazin-3-yl]-2-(2-methoxyphenyl)-acetamide* ***(25)***.

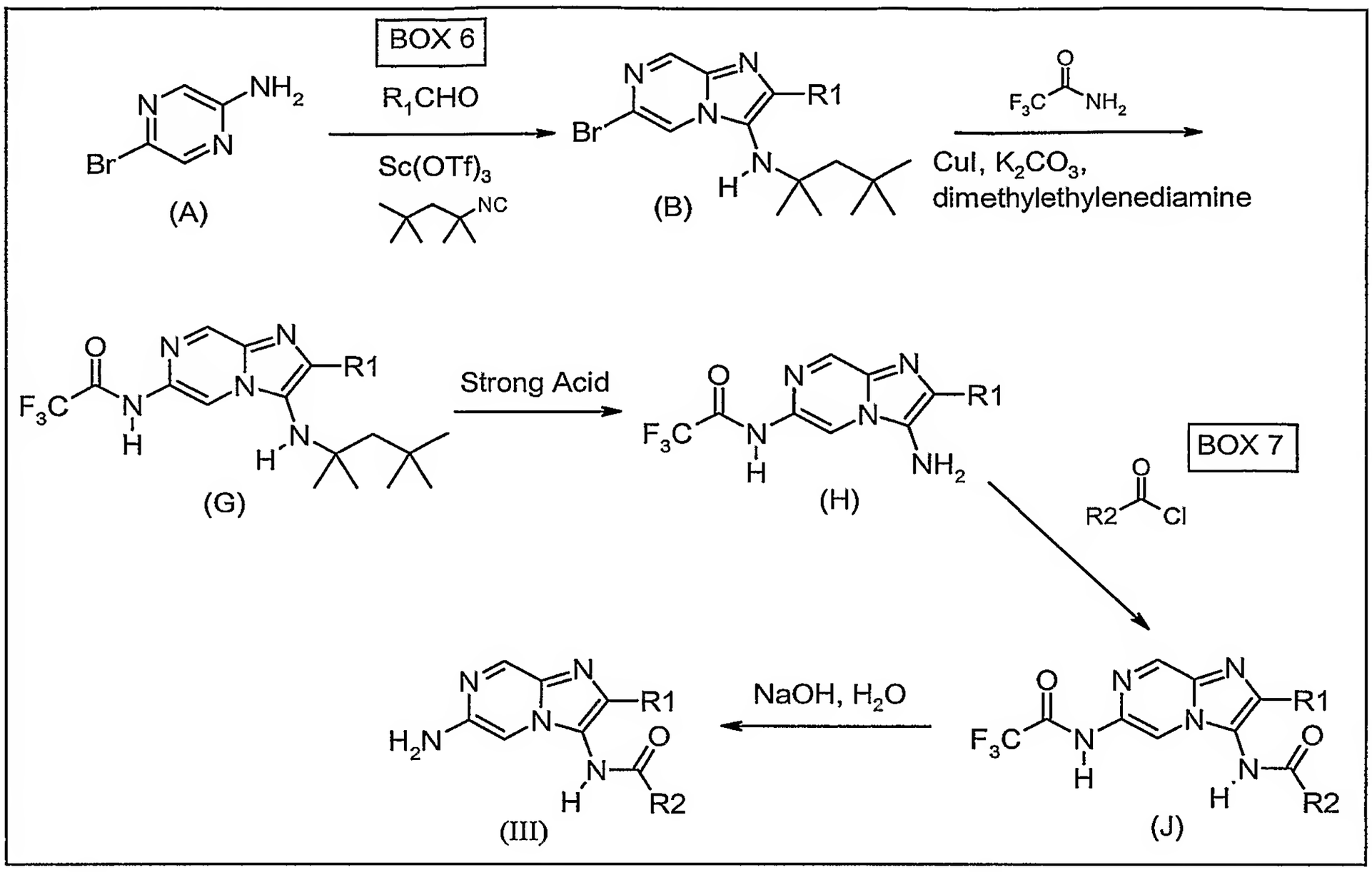


(25)

Yield 36.6 mg, 36%; HPLC 100%; ^{1}H NMR (250 MHz, DMSO) δ 10.65 (s, 1H), 10.40 (s, 1H), 8.93 (d, *J* = 1.4 Hz, 1H), 8.85 (d, *J* = 1.4 Hz, 1H), 7.76-6.87 (m, 13H), 3.83 (s, 3H), 3.70 (s, 2H), 2.12 (s, 3H); MS (ES) 508 $[M+H]^+$.

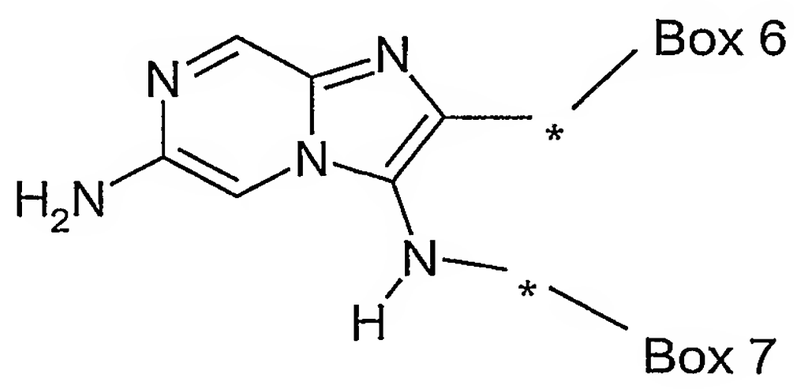
<u>Scheme for synthesising compounds of formula (III) (PS109)</u>

A general scheme for introducing substituents to produce compounds of SFK11 PS109, is as follows:



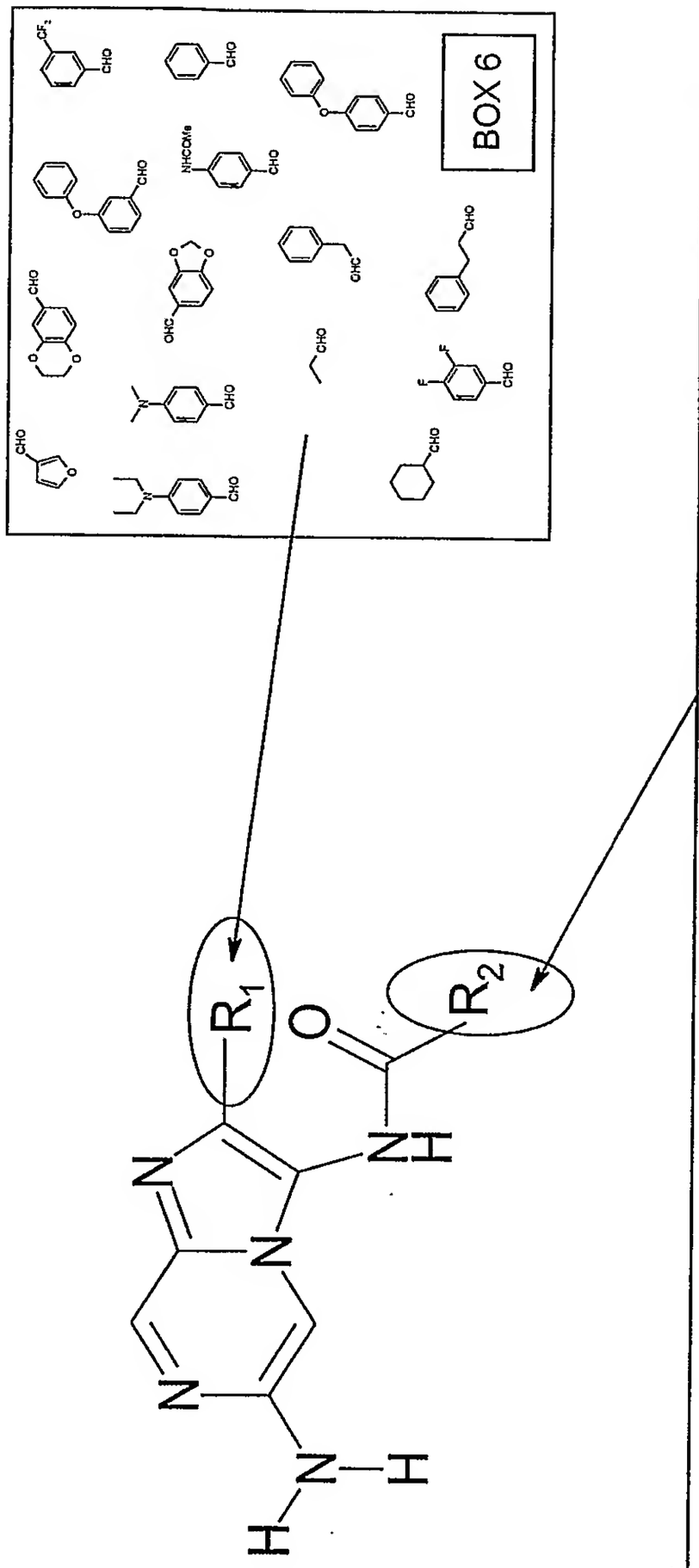
2-Amino-5-bromopyrazine (A) can be converted to the substituted 3-amino-6-bromoimidazo[1,2-a]pyrazines (B) using the aldehydes described in Box 6. The intermediates (B) can be reacted with trifluoroacetamide to give amides (G) and then deprotected to give primary amines (H). The resultant amines can be acylated with acid chlorides prepared from the acids described in Box 7 to give amides (J) and deprotected to give the primary amines (III).

The permitted substituents at positions R_1 and R_2 are shown in Boxes 1 and 2 respectively, in the following schematic diagram.



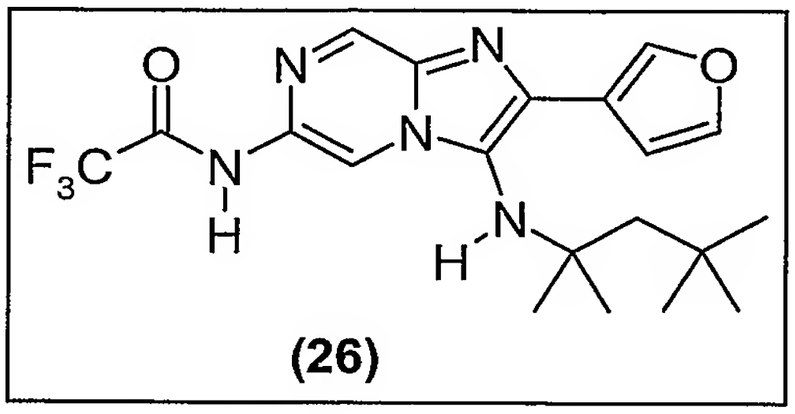
SFK11

Scatter Diagram


BOX 6
BOX 7
R1
R2
O
NH
N
N
N
H
H

General Procedures

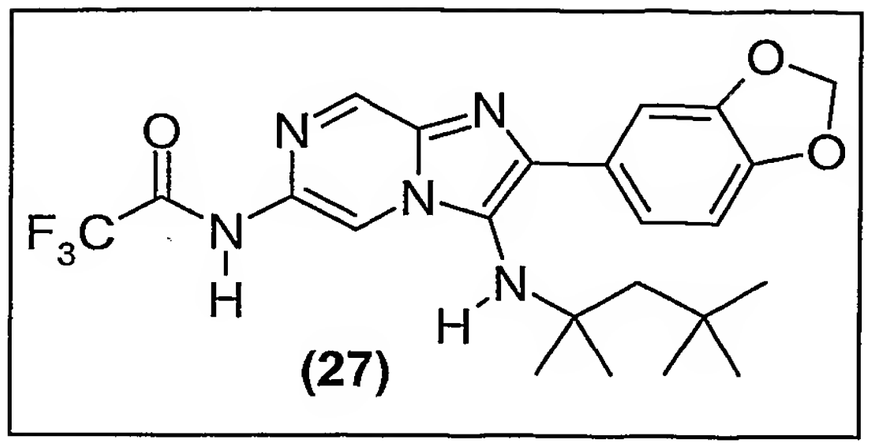
Typical example of compound of formula (G), as described in general reaction scheme; *2,2,2-trifluoro-N-[2-furan-3-yl-3-(1,1,3,3-tetramethyl-butylamino)imidazo [1,2-a]pyrazin-6-yl]-acetamide* ***(26)***.



(26)

(2-(3-Furyl)-6-bromoimidazo[1,2-a]pyrazin-3-yl)-(1,1,3,3-tetramethylbutyl)amine (11.7 g, 30 mmol), trifluoroacetamide (5.0 g, 45 mmol), copper (I) iodide (0.86 g, 4.5 mmol), *N,N'*-dimethylethylenediamine (0.5 mL, 4.7 mmol), copper bronze (0.065 g, 1.0 mmol) and potassium carbonate (8.3 g, 60 mmol) were weighed into a 100 mL round-bottom flask. After the flask was evacuated and flushed with nitrogen (× 3), toluene (35 mL) was added and the reaction mixture heated (100 °C) for 24 hours. After LCMS analysis showed that all the starting material had been consumed, the reaction mixture was diluted with ethyl acetate and filtered through a short plug of silica. The filtrate was concentrated and the residue purified by column chromatography to yield the desired amide **(26)** as a yellow solid (9.0 g, 71%). HPLC 93%; ^{1}H NMR (250 MHz, DMSO) δ 12.16 (s, 1H), 9.09 (s, 1H), 8.85 (s, 1H), 8.31 (s, 1H), 7.76 (s, 1H), 7.09 (s, 1H), 4.65 (s, 1H), 1.67 (s, 2H), 1.04 (s, 6H), 1.03 (s, 9H); MS (APCI) 424 $[M+H]^+$.

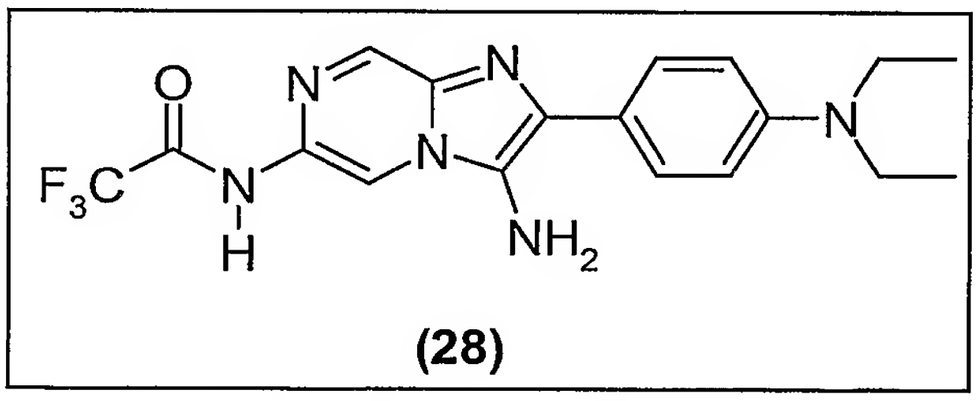
Typical example of compound of formula (G), as described in general reaction scheme; *N-[2-benzo[1,3]dioxol-5-yl-3-(1,1,3,3-tetramethylbutylamino)imidazo[1,2-a]pyrazin-6-yl]-2,2,2-trifluoroacetamide* ***(27)***.



(27)

Yield 2.85 g, 15%; HPLC 95%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.73 (s, 1H), 8.55 (s, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 2H), 3.20 (s, 1H), 1.64 (s, 2H), 1.08 (s, 9H), 1.03 (s, 6H); MS (APCI) 478 $[M+H]^+$.

Typical example of compound of formula (H), as described in general reaction scheme; *N-[3-amino-2-(4-diethylaminophenyl)-imidazo[1,2-a]pyrazin-6-yl]-2,2,2 -trifluoroacetamide* ***(28).***

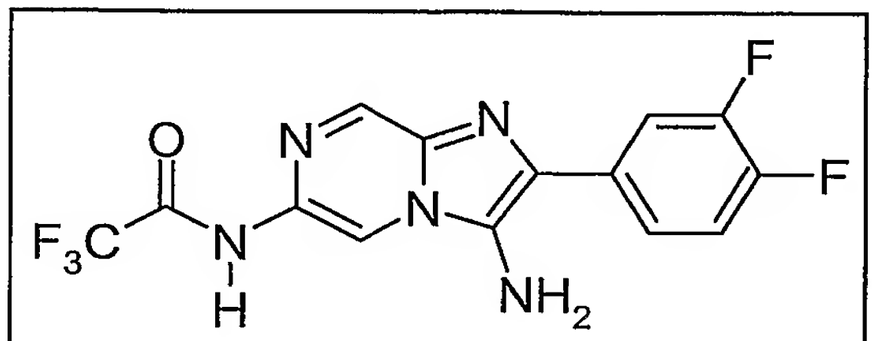


(28)

N-[2-(4-Diethylaminophenyl)-3-(1,1,3,3-tetramethylbutylamino)-imidazo[1,2-a]pyrazin-6-yl]-2,2,2-trifluoroacetamide (2.5 g, 5.0 mmol) was weighed into a 100 mL round-bottom flask and was dissolved in 4M HCl/dioxane (20 mL). After stirring at room temperature for 16 hours, the solution was analysed by LCMS and determined to have reached completion. The reaction mixture was concentrated and the crude residue was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was separated, dried and concentrated to give the desired amine **(28)** as a dark yellow solid (1.3 g, 67%). HPLC 100%; ^{1}H

NMR (250 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.68 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 2H), 3.42 (q, *J* = 7.0 Hz, 4H), 1.21 (t, *J* = 7.0 Hz, 6H); MS (APCI) 393 $[M+H]^+$.

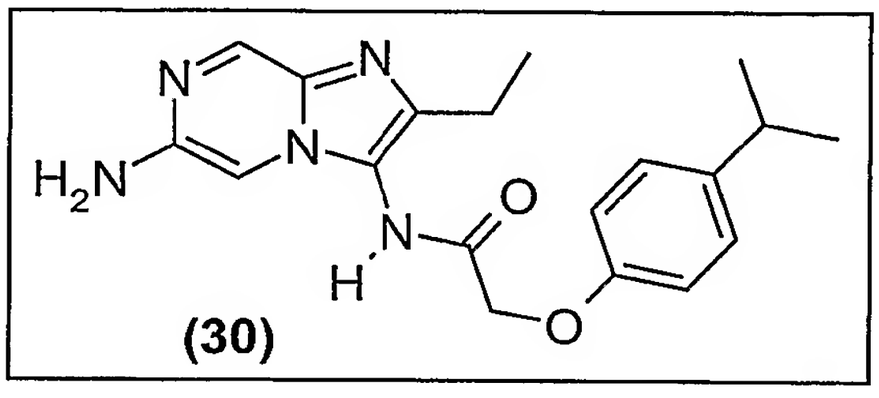
Typical example of compound of formula (H), as described in general reaction scheme; *N-[3-amino-2-(3,4-difluorophenyl)-imidazo[1,2-a]pyrazin-6-yl]-2,2,2-trifluoroacetamide* ***(29)***.



(29)

Yield 1.6 g, 97%; HPLC 89%; ^1H NMR (250 MHz, DMSO) δ 11.98 (s, 1H), 8.82 (s, 1H), 8.74 (s, 1H), 7.92 (m, 1H), 7.81 (m, 1H), 7.49 (m, 1H), 5.95 (s, 2H); MS (APCI) 356 $[M-H]^-$.

Typical example of compound of formula (III), as described in general reaction scheme; *N-(6-amino-2-ethylimidazo[1,2-a]pyrazin-3-yl)-2-(4-isopropylphenoxy)-acetamide* ***(30)***.

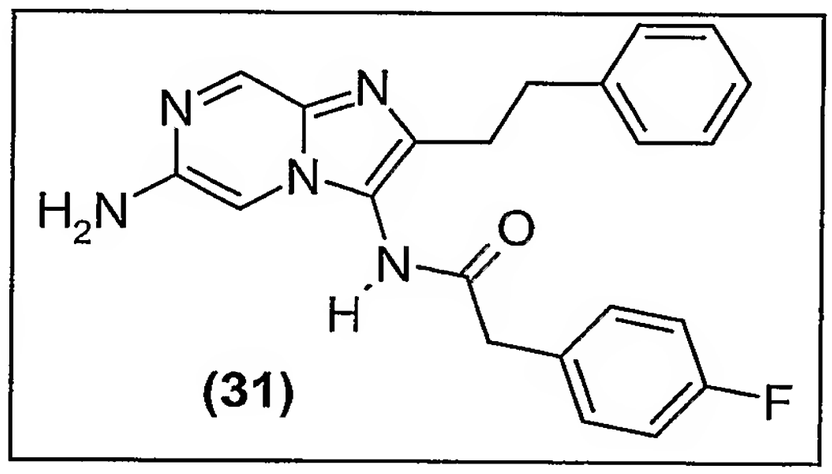


(30)

To a 'Stem' reaction tube containing (4-isopropylphenoxy)acetic acid (58.3 mg, 0.3 mmol) in THF (0.5 mL) was added oxalyl chloride (25 μL, 0.3 mmol) and a drop of DMF. The reaction mixture was flushed with

nitrogen, capped and shaken for 2 hours. Solid *N*-(3-amino-2-ethyl-imidazo[1,2-a]pyrazin-6-yl)-2,2,2-trifluoroacetamide (55 mg, 0.2 mmol) and a solution of diisopropylethylamine (70 μL, 0.4 mmol) in THF (0.5 mL) was added to the acid chloride solution and the reaction again flushed with nitrogen and capped. After heating to 60 °C for 16 hours, the tubes were uncapped and a solution of sodium hydroxide (40 mg, 1 mmol) in H_2O (0.5 mL) added to the reaction mixture which was heated for a further 4 hours. The tubes were allowed cool and the contents diluted with DMSO (0.5 mL), filtered and purified by reverse-phase preparative HPLC to yield the desired amide **(30)** as a pale yellow solid (30.4 mg, 43%). HPLC 100%; MS (ES) 356 $[M+H]^+$.

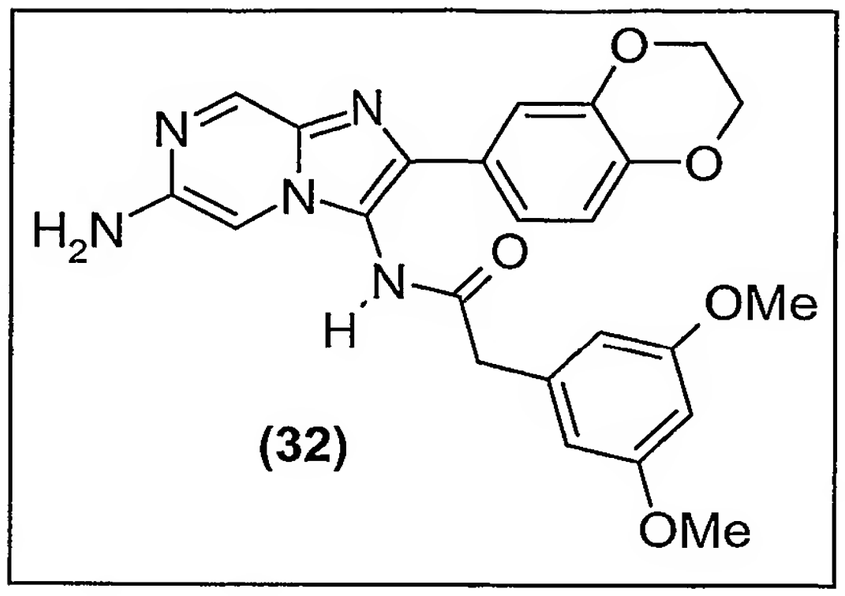
Typical example of compound of formula (III), as described in general reaction scheme; *N-(6-amino-2-phenethylimidazo[1,2-a]pyrazin-3-yl)-2-(4-fluorophenyl)-acetamide* ***(31)***.



(31)

Yield 28.4 mg, 36%; HPLC 100%; MS (ES) 390 $[M+H]^+$.

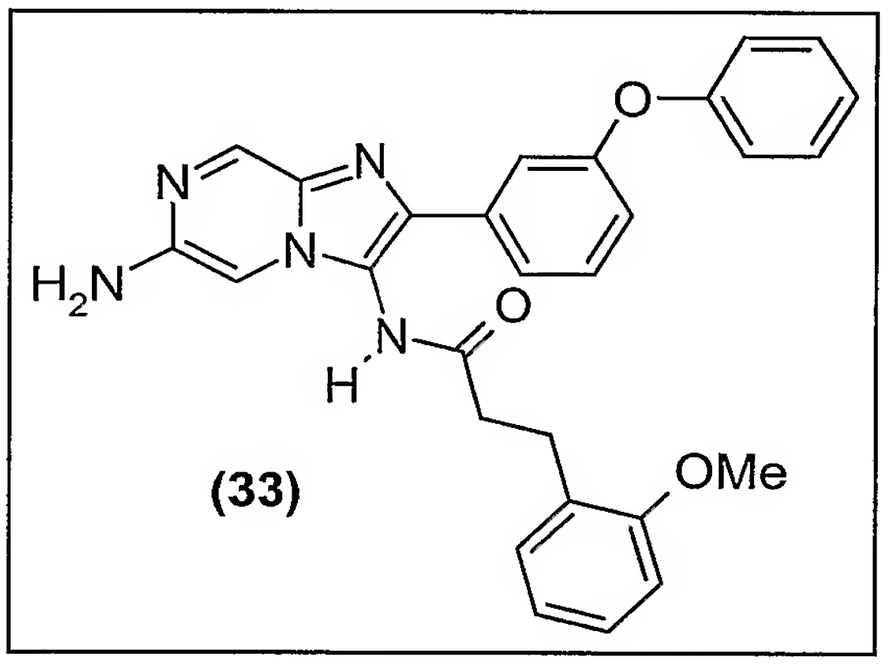
Typical example of compound of formula (III), as described in general reaction scheme; *N-[6-amino-2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-imidazo[1,2-a]pyrazin-3-yl]-2-(3,5-dimethoxyphenyl)-acetamide* ***(32)***.



(32)

Yield 28.0 mg, 30%; HPLC 95%; MS (ES) 462 $[M+H]^+$.

Typical example of compound of formula (III), as described in general reaction scheme; *N-[6-amino-2-(3-phenoxyphenyl)-imidazo[1,2-a]pyrazin-3-yl]-3-(2-methoxyphenyl)-propionamide* ***(33)***.



(33)

Yield 27.0 mg, 28%; HPLC 100%; MS (ES) 480 $[M+H]^+$.

<u>Purification Conditions</u>

All compounds have a minimum purity level ≥ 80% as measured by LCMS at 254 nm.

The columns used for the preparative HPLC purification of the various scaffolds are outlined in Table 1:

Table 1

Scaffold	Column
All compounds	Varian Polaris 10μm C18-A 150 x 21.2mm

The gradient used for the preparative HPLC purification of all compounds was 95% water (10mmol NH_3HCO_3) 5% Acetonitrile for 1 min to 5% water (10mmol NH_3HCO_3) / 95% Acetonitrile over 8.0 min then held at 5% water (10mmol NH_3HCO_3) / 95% Acetonitrile for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

A flow rate of 25 ml/min was used.

The conditions used for the analytical HPLC analysis following preparative HPLC purification are outlined in Table 2:

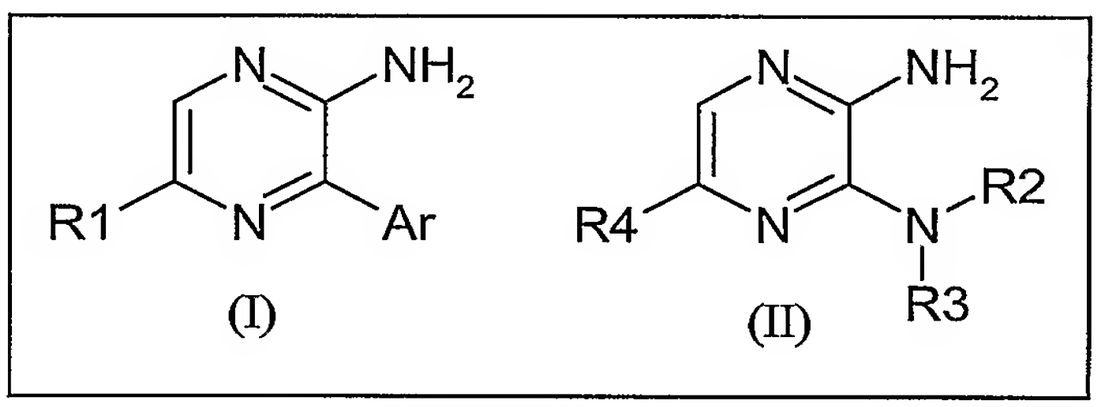
Table 2

Conditions	Detection
Column: Waters Xterra® Prep MS C18 5μm 4.6 x 100mm. **Gradient**: 95% water (10 mM NH_3HCO_3) / 5% ACN for 0.5 min then 95% water (10 mM NH_3HCO_3) / 5% ACN to 2% water (10 mM NH_3HCO_3) / 98% ACN over 3.5 min. Held at 2% water (10 mM NH_3HCO_3) / 98% ACN for 0.5 min. The solvent mixture is then returned to the initial conditions over 0.1 min and the system allowed to re-equilibrate for 0.2 min. **Flow rate:** 2.0 ml/min. **Temperature:** 30 °C. **Injection volume:** 5 μm partial loop.	UV detection at 254 nm (diode array range 210-280nm). **Electrospray ionisation**: Cone voltage: 30 V. Cone temperature: 20 °C. Source temperature 150 °C. RF lens voltage: 0.0 V. Ion energy: 0.5 eV. Multiplier: 650 V.

LIBRARY SFK14

SFK14 is designed to have a broad focus on the tyrosine and serine/threonine kinases that recognise typical mono-and bicyclic heterocyclic ligands for the ATP binding site. The central scaffold is based on a novel application of the 3-aminopyrazine scaffold bearing substitutents at the 2 and 6 positions. Each scaffold has been docked into the ATP-binding region of a variety of kinases including Zap-70, CDK2, p38 MAP kinase, FGFr1, PKA, Hck and Erk2 and all have shown they are capable of mimicking the characteristic double H-bonding system seen between ATP and the enzyme backbone in protein kinase ATP sites.

The invention provides a compound library comprising or consisting of structurally related compounds of general formula (I) and (II):

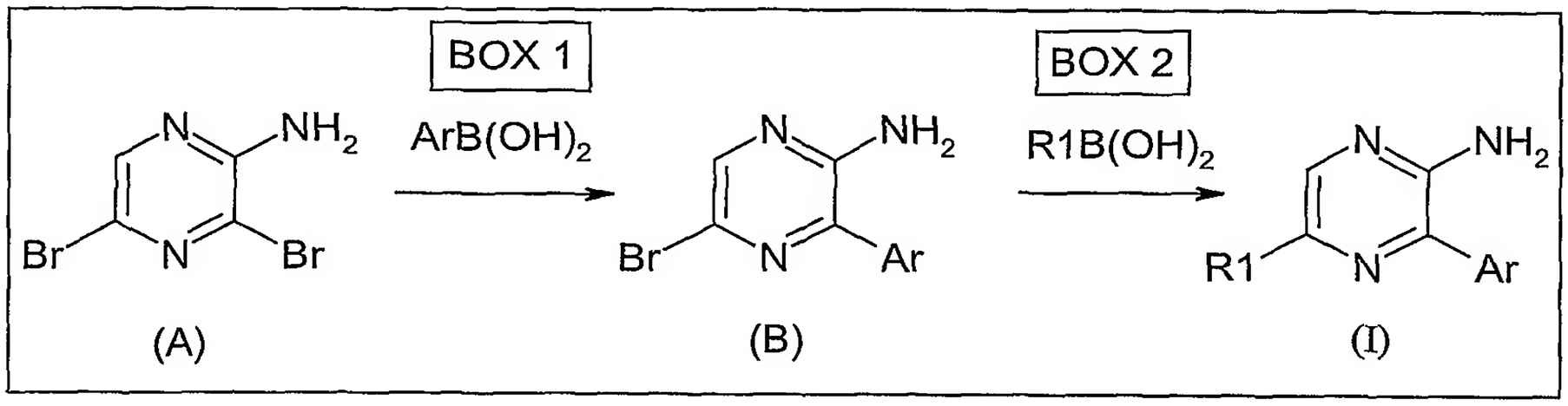


Wherein Ar is aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and contains one or more heteroatoms; R_1 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic

aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; R_2 is hydrogen; R_3 is alkyl having from 1 to 20 carbon atoms which may be linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and R_4 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms. R_2 and R_3 may also be joined to form the same ring system.

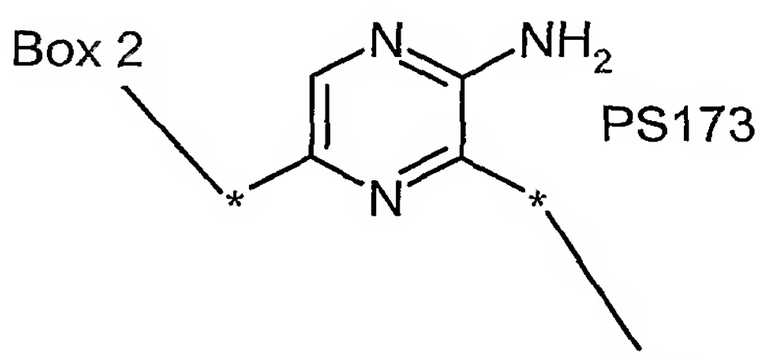
Scheme for synthesising compounds of formula (I) (PS173)

A general scheme for introducing substituents to produce compounds of SFK14 PS173 is as follows:



2-Amino-3,5-dibromopyrazine (A) can be reacted with the boronic acids described in Box 1. The resultant compound (B) can be then be reacted with the boronic acids described in Box 2.

The permitted substituents at position Ar and R1 are shown in Boxes 1 and 2 respectively, in the following schematic diagram.

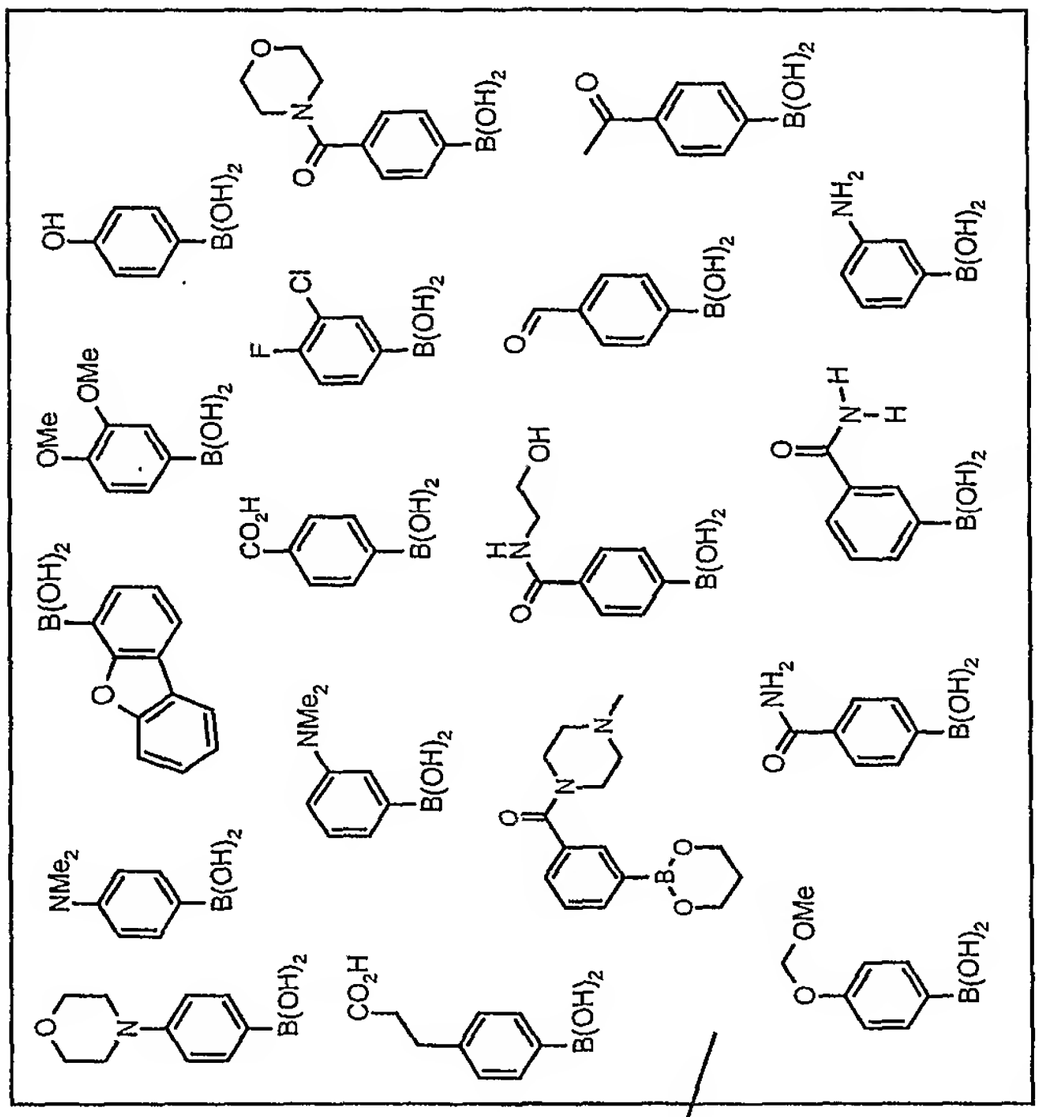


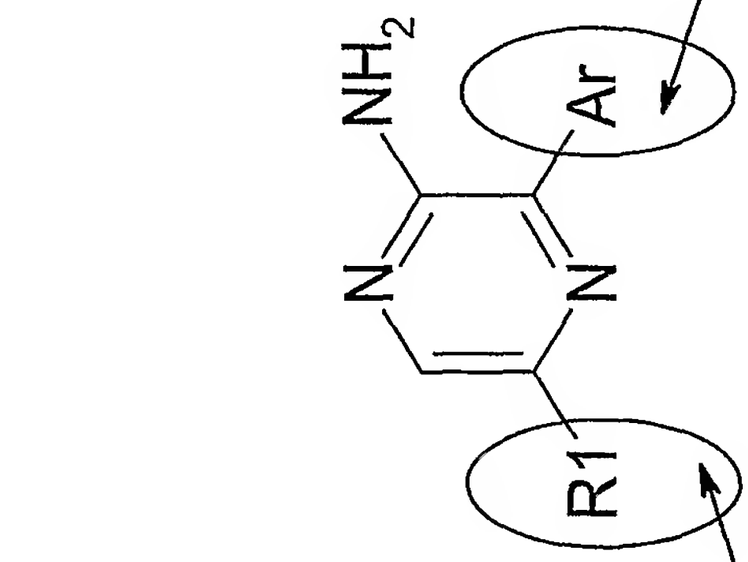
SFK14

Scatter Diagram

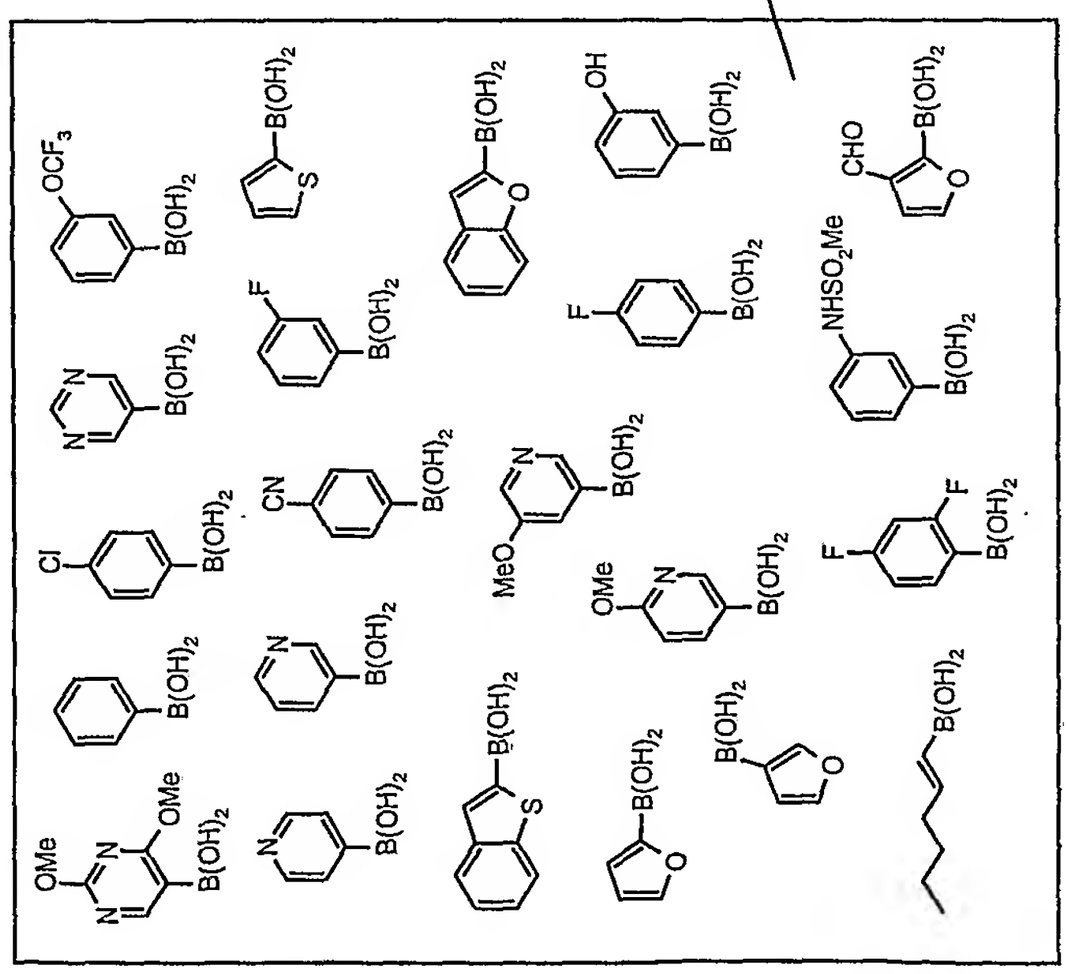
Box 1

BOX 1



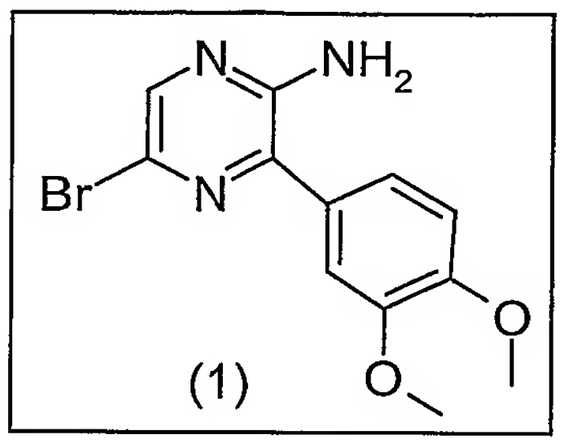


BOX 2



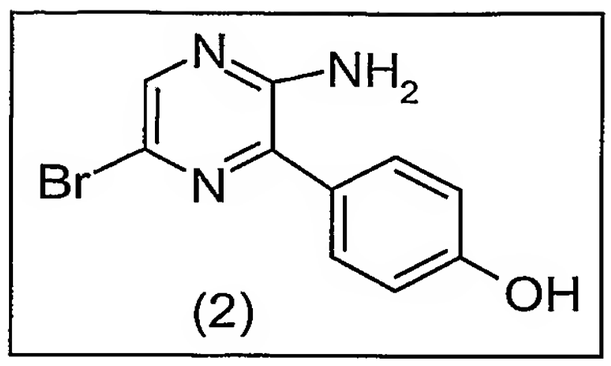
General Procedures

Typical example of compound of formula (B), as described in general reaction scheme; *5-bromo-3-(3,4-dimethoxyphenyl)pyrazine-2-amine* ***(1)***.



To a mixture of 3-amino-2, 6-dibromopyrazine (18 mmol, 1eq.) and boronic acid (21.6 mmol, 1.2 eq.) in 40 ml degassed DMF was added a 30 ml 1.5 M degassed solution of sodium carbonate (45 mmol, 2.5 eq.). The mixture was then degassed for a further 5 mins by bubbling N_2 through. To the latter mixture, a yellow suspension of triphenylphosphine (2.7 mmol, 0.15 eq.) and palladium acetate (0.9 mmol, 0.05 eq.) in degassed dioxane (18 ml) was added under a nitrogen atmosphere. After the addition was complete, the reaction mixture was heated overnight at 80^0C with stirring. The reaction mixture was diluted with ethyl acetate (50 ml) and the solid was filtered. The filtrate was washed with water and brine and the organic solution was then filtered through a short pad of silica and washed with ethyl acetate. The filtrate was evaporated to dryness under reduced pressure and the crude organic residue was triturated with diethyl ether to give the required compound as a yellow solid (1.72g, 30%). ^{1}H NMR ($CDCl_3$): δ^H 7.87 (s, 1H, PyzH), 7.07-7.03 (m, 2H, ArH), 6.91 (d, J=8 Hz, 1H, ArH), 6.26 (brs, exc., 2H, NH_2), 3.65 (s, 6H, 2xCH_3); MS (APCI) m/z: 310&312 isotopes, (100%, $[M+H]^+$), 351&353 isotopes (20%, $[M+CH_3CN]^+$), 232 (24%, $[M+H-Br]^+$); HPLC 96%.

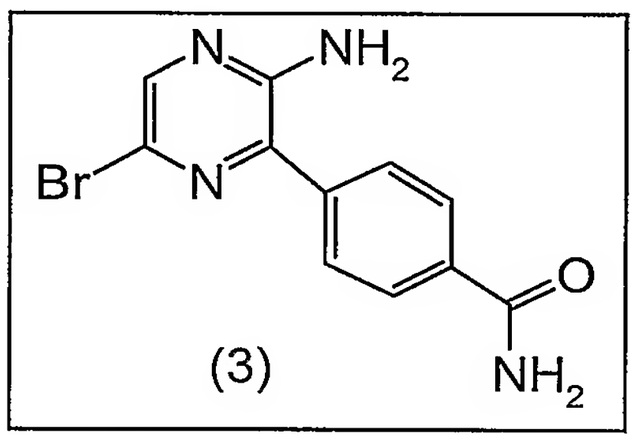
Typical example of compound of formula (B), as described in general reaction scheme; *4-(3-amino-6-bromopyrazin-2yl)phenol* ***(2)***.



(2)

Yield (4.22 g, 87%); ^{1}H NMR (DMSO): δ^H 9.83 (brs, exc., 1H, OH), 7.98 (s, 1H, PyzH), 7.52 (d, J=9Hz, 2H, ArH), 6.84 (d, J=9Hz, 2H, ArH), 6.33 (brs, exc., 2H, NH_2); MS (APCI) m/z: 264&266 isotopes (100%,$[M-H]^-$); HPLC 98%.

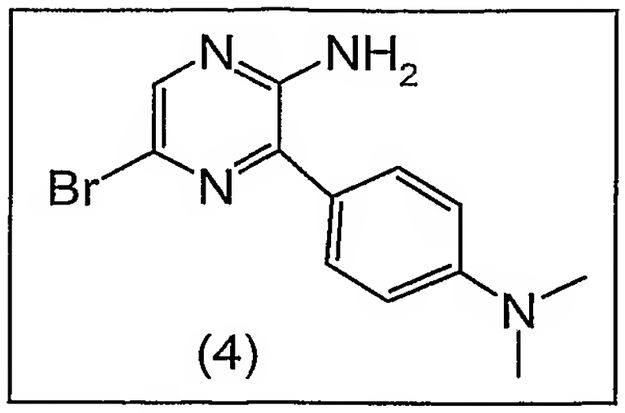
Typical example of compound of formula (B), as described in general reaction scheme; *4-(3-amino-6-bromopyrazin-2-yl)benzamide* ***(3).***



(3)

Yield (2.5 g, 48%); ^{1}H NMR (DMSO): δ^H 8.10 (brs, exc., 2H, $CONH_2$), 7.98 (d, J=8.5 Hz, 2H, ArH), 7.73 (d, J=8.5Hz, 2H, ArH), 7.46 (s, 1H, PyzH), 6.54 (brs, exc., 2H, NH_2); MS (APCI) m/z: 293&295 isotopes,(100%, $[M+H]^+$), 334&336 isotopes (35%, $[M+ CH_3CN]^+$), 215 (35%, $[M+H-Br]^+$); HPLC 96%.

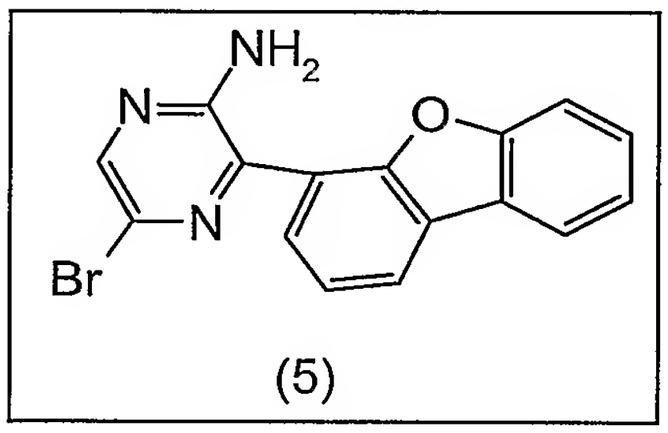
Typical example of compound of formula (B), as described in general reaction scheme; *5-bromo-3-[4-(dimethylamino)phenyl]pyrazine-2-amine* ***(4)***.



(4)

Yield (3.58 g, 68%); ^{1}H NMR (DMSO): δ^H 7.92 (s, 1H, PyzH), 7.56 (d, J=9 Hz, 2H, Ar), 6.78 (d, J=9Hz, 2H, Ar), 6.28 (brs, exc., 2H, NH_2), 2.96(s, 6H, CH_3x2); MS (APCI) m/z: 293&295 isotopes,(100%, $[M+H]^+$), 334&336 isotopes (15%, $[M+ CH_3CN]^+$), 215 (16%, $[M+H-Br]^+$); HPLC 99%.

Typical example of compound of formula (B), as described in general reaction scheme; *5-bromo-3-dibenzo[b,d]furan-4-ylpyrazin-2-amine* ***(5)***.



(5)

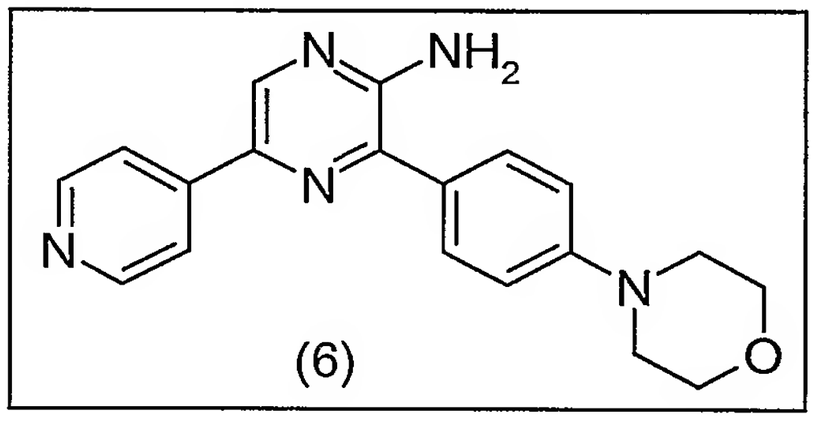
Yield (3 g, 49%); ^{1}H NMR (DMSO): δ^H 8.25 (dd, J=7.5 Hz & 1.5 Hz, 1H, ArH), 8.21-8.18 (m, sH, ArH), 8.19 (s, 1H, ArH), 7.71 (d, J=8Hz, 1H, ArH), 7.61-7.36 (m, 5H, ArH), 6.51 (brs, exc., 2H, NH_2); MS (APCI) m/z: 340&342 isotopes,(100%, $[M+H]^+$), 381 & 383 isotopes (47%, $[M+ CH_3CN]^+$), 262 (31%, $[M+H-Br]^+$); HPLC (94%).

<u>General procedure for the synthesis of compounds of formula (I).</u>

To a solution of compound of formula (B) in degassed DMF (0.3mmol, 1 eq., 0.5ml) was added a solution of boronic acid in DMF (0.36mmol, 1.2 eq., 0.6ml) and 1.5M Na_2CO_3 (degassed aq.) solution (0.75mmol, 2.5 eq., 0.5 ml). A solution of palladium (II) acetate (0.015 mmol, 0.05 eq., 168mg) and triphenylphosphine (0.045 mmol, 0.15 eq., 588mg) in

degassed 1,4-dioxane (15ml) was freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml, yellow suspension) was then added to the reaction vessel under a nitrogen atmosphere and the contents were heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative reverse phase HPLC.

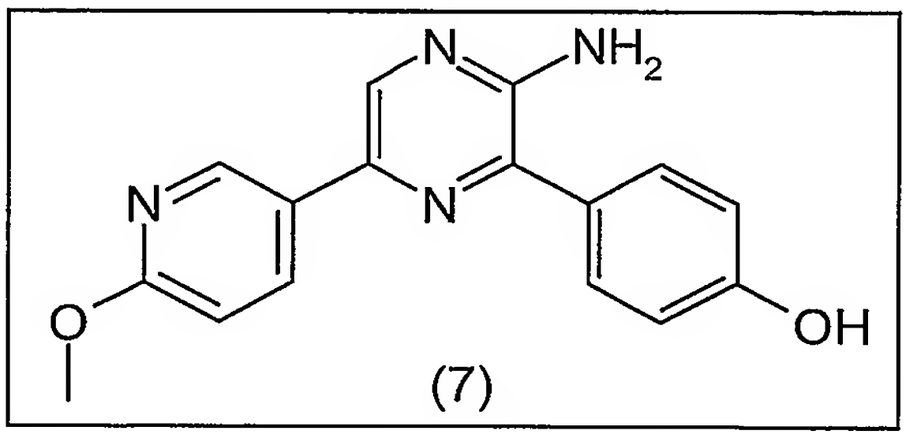
Typical example of compound of formula (I), as described in general reaction scheme; *3-(4-morpholin-4-ylphenyl)-5-pyridin-4-ylpyrazin-2-amine* ***(6)***.



(6)

Yield 50.6mg, 51%; ^{1}H NMR (DMSO): δ^H 8.63 (s, 1H, PyzH), 8.57(dd, J=5Hz &1.5 Hz, 2H, ArH), 7.94(d, J=5Hz, 2H, ArH), 7.70 (d, J=9Hz, 2H, ArH), 7.06 (d, J=9Hz, 2H, ArH), 6.57 (brs, exc., 2H, NH_2), 3.77-3.73 (m, 4H, 2xCH_2); MS (ES) m/z: 334,(100%, $[M+H]^+$); HPLC 100%.

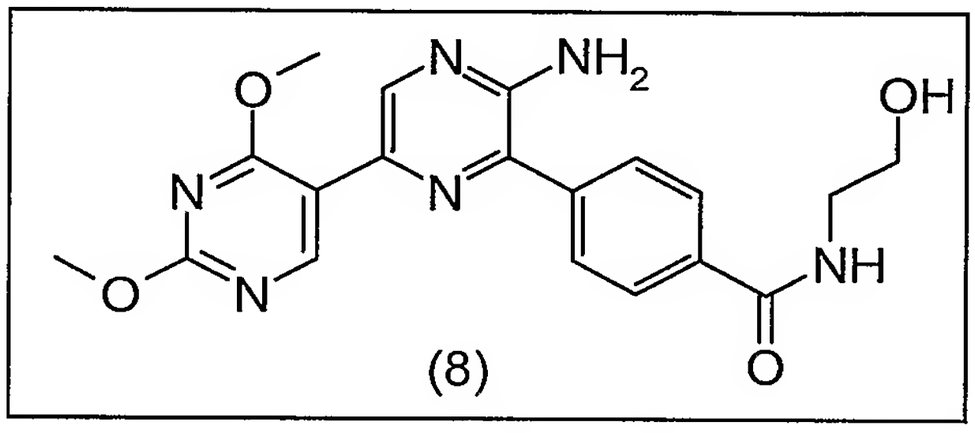
Typical example of compound of formula (I), as described in general reaction scheme; *4-[3-amino-6-(6-methoxypyridin-3-yl)pyrazine-2-yl]phenol* ***(7)***.



(7)

Yield 47mg, 53%; ^{1}H NMR (DMSO): δ^H 9.75 (s, exc., 1H, OH), 8.74(d, J=1.5Hz, 1H, PyH), 8.44 (s, 1H, PyzH), 8.24(dd, J=8.5Hz&1.5Hz, 1H, PyH), 7.63 (d, J=8.5Hz, 2H, ArH), 6.87 (d, J=8.5Hz, 3H, 2xArH+1xPyH), 6.20 (brs, exc., 2H, NH_2), 3.87 (s, 3H, CH_3); MS (ES) m/z: 295 (100%, $[M+H]^+$); HPLC 100%.

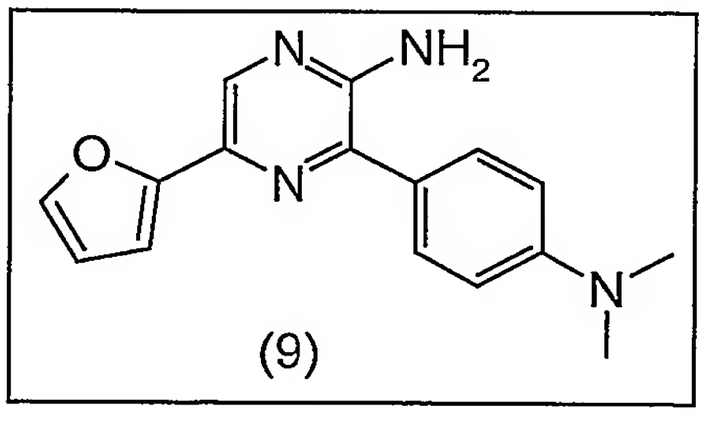
Typical example of compound of formula (I), as described in general reaction scheme; 4-[3-amino-6-(2,4-dimethoxy-pyrimidin-5-yl)-Pyrazin-2-yl]-N-(2-hydroxy-ethyl)-benzamide ***(8)***.



(8)

Yield 54.5mg, 46%; ^{1}H NMR (DMSO): δ^H 8.77 (s, 1H, ArH), 8.55(t, exc., J=5.5Hz, 1H, NH), 8.44 (s, 1H, ArH), 7.97 (d, J=8.5Hz, 2H, ArH), 7.86 (d, J=8.5 Hz, 2H, ArH), 6.47 (brs, exc., 2H, NH_2), 4.76 (t, exc., J=5.5Hz, 1H, OH), 4.01 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.51 (q, J=5.5Hz, 2H, CH_2), 3.37-3.31 (m, 2H, CH_2); MS (ES) m/z: 397,(100%, $[M+H]^+$); HPLC 100%.

Typical example of compound of formula (I), as described in general reaction scheme; *3-[4-(dimethylaminophenyl]-5-(2-furyl)pyrazin-2-amine* ***(9)***.

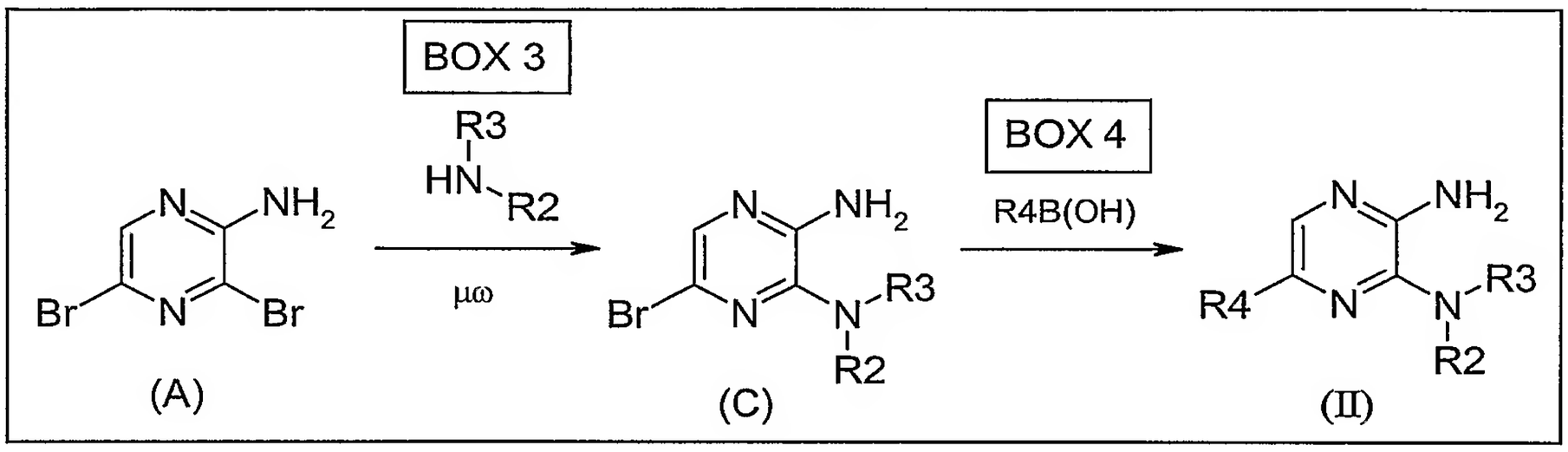


(9)

Yield 31.3mg, 37%; ^{1}H NMR (DMSO): δ^H 8.20 (s, 1H, PyzH), 7.71(dd, J=2Hz&1Hz, 1H, FurH), 7.61 (d, J=9Hz, 2H, ArH), 6.82 (d, J=9Hz, 2H, ArH), 6.80-6.78 (m, 1H, ArH), 6.56 (dd, J=3Hz&2Hz, 1H, FurH), 6.22 (brs, exc., 2H, NH_2), 2.96 (s, 6H, CH_3x2); MS (ES) m/z: 281(100%, $[M+H]^+$); HPLC 100%.

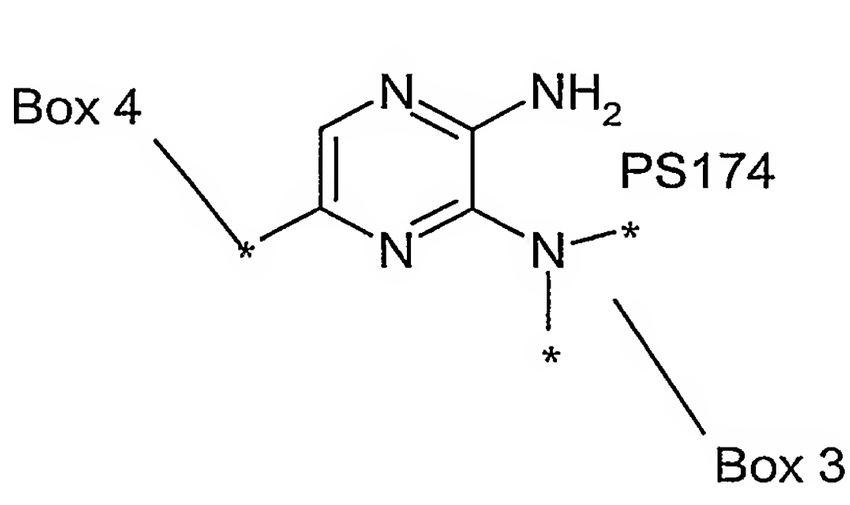
Scheme for synthesising compounds of formula (II) (PS174)

A general scheme for introducing substituents to produce compounds of SFK 14 PS174 is as follows:



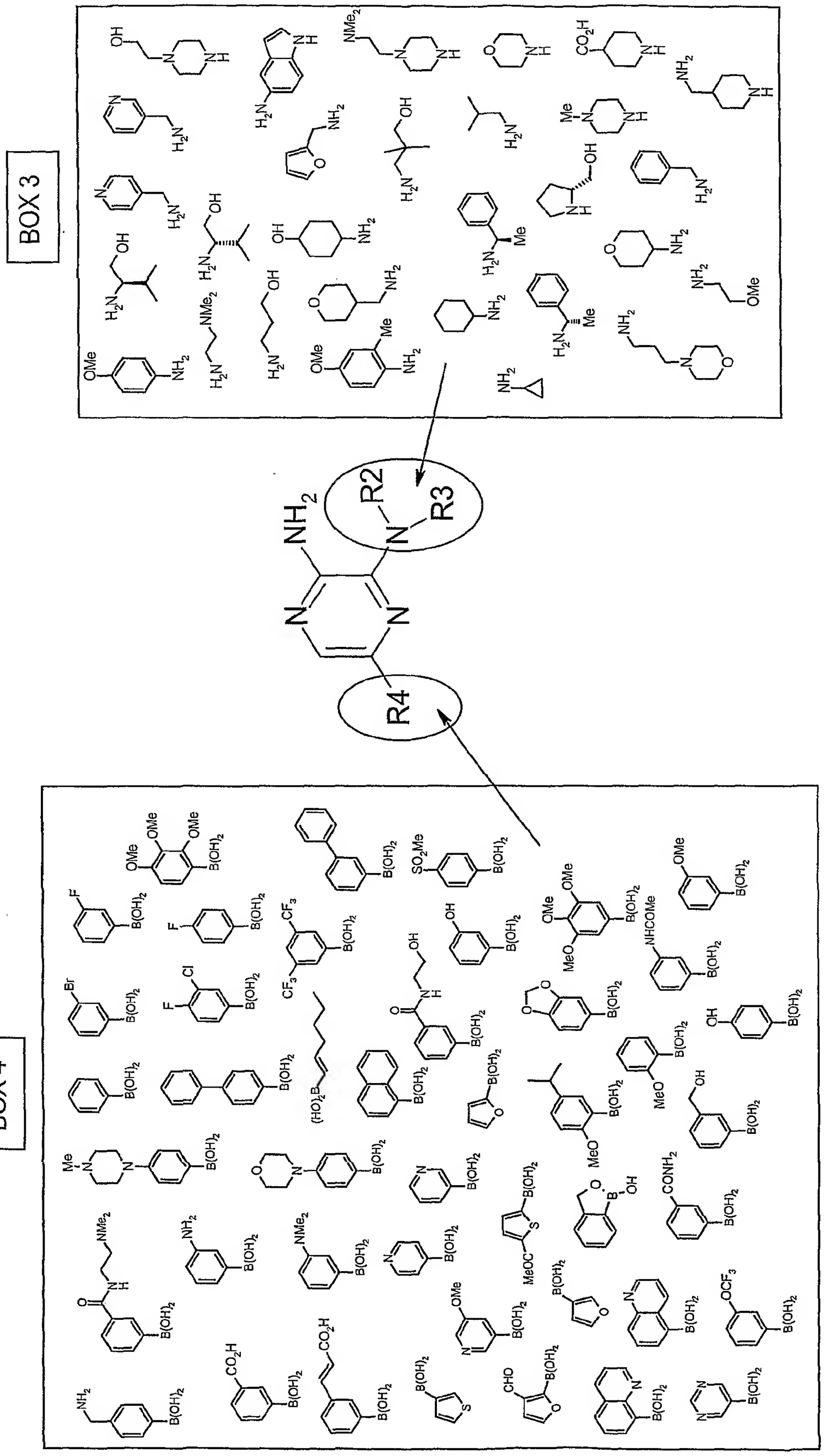
The C3 bromine of 2-amino-3,5 dibromopyrazine (A) can be selectively displaced with the primary and secondary amines or anilines described in Box 3. The resultant compounds (C) can then be reacted with the boronic acids described in Box 4 to form the desired targets (II).

The permitted substituents at position R2, R3 and R4 are shown in Boxes 3 and 4 respectively, of the following diagrams.



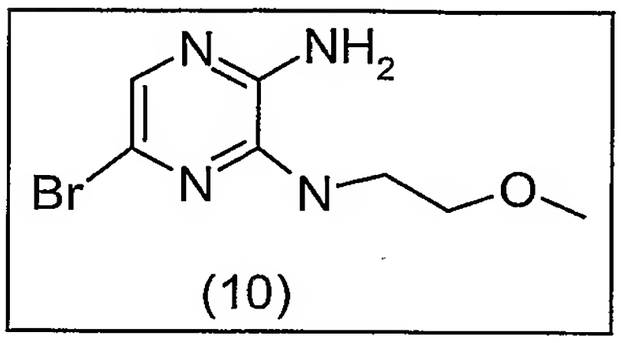
SFK 14

Scatter Diagram


BOX 3
BOX 4
R2
R3
R4

General procedures

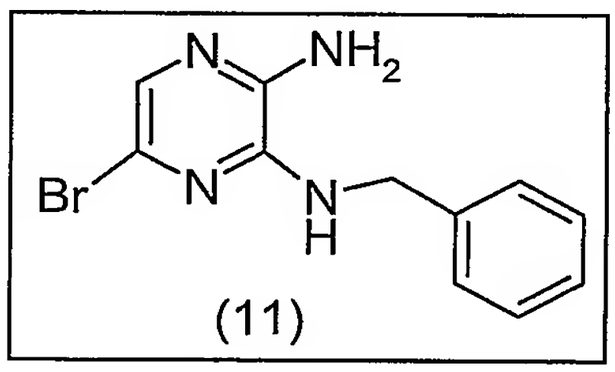
Typical example of compound of formula (C), as described in general reaction scheme; *5-bromo-N^3-(2-methoxyethyl)pyrazine-2,3-diamine* ***(10)***.



(10)

A mixture of 2-amino-3, 5-dibromopyrazine (6 mmol, 1eq.), primary amine (6.6 mmol, 1.1 eq.) and DIPEA (6.6 mmol, 1.1 eq.) in ethanol (1ml) was placed in the CEM Discover and heated at 180 ^{0}C (70W) for 25min. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate. The organic solution was washed with water and brine then decolorised by refluxing the solution with charcoal for 1 hour. The unwanted solid was filtered off and the solvent removed under reduced pressure. The crude organic residue was triturated with hexane to give the desired product as a yellow solid (0.89g, 69%); ^{1}H NMR ($CDCl_3$): δ^H 7.42 (s, 1H, PyzH), 4.98 (brs, exc., 1H, NH), 4.47 (brs, exc., 2H, NH_2), 3.61 (m, 4H, CH_2), 3.38 (s, 3H, CH_3); MS (APCI) m/z: 247 & 249 isotopes, (83%, $[M+H]^+$), 215&217 isotopes, (100%, $[M- OCH_3+H]^+$), 288 & 290 isotopes, (7%, $[M+CH_3CN]^+$); HPLC 99%.

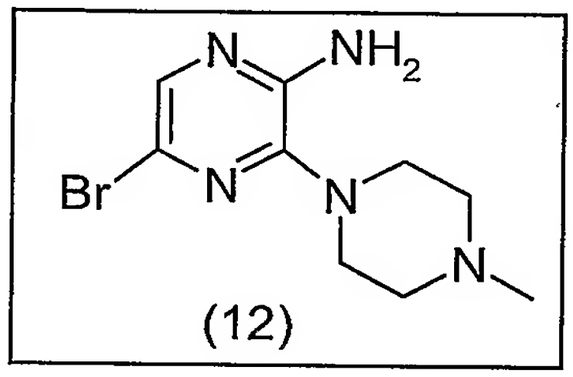
Typical example of compound of formula (C), as described in general reaction scheme; *N^3-benzyl-5-bromopyrazine-2,3-diamine* ***(11)***.



(11)

Yield (1.33 g, 80%); ^{1}H NMR ($CDCl_3$): δ^H 7.29 -7.46 (m, 5H, ArH), 7.43 (s, 1H, PyzH), 4.69 (brs, exc., 1H, NH), 4.56 (d, J=6 Hz, 2H, CH_2), 4.31 (brs, exc., 2H, NH_2); MS (APCI) m/z: 279&281 isotopes, (100%, $[M+H]^+$) HPLC 94%.

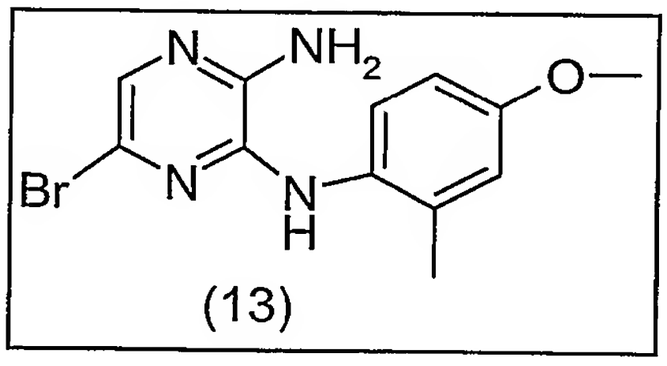
Typical example of compound of formula (C), as described in general reaction scheme; *5-bromo-3-(4-methylpiperazin-1-yl)pyrazine-2-amine* ***(12)***.



(12)

Yield (0.75g, 46%); ^{1}H NMR ($CDCl_3$): δ^H 7.66 (s, 1H, PyzH), 4.59 (brs, exc., 2H, NH_2), 3.16 (brs, 4H, CH_2), 2.49 (brs, 4H, CH_2), 2.28 (s, 3H,CH_3); MS (APCI) m/z: 272&274 isotopes, (100%, $[M+H]^+$); HPLC 99%.

Typical example of compound of formula (C), as described in general reaction scheme; *N^3-(4-methoxy-2-methylphenyl)pyrazine-2,3-diamine* ***(13)***.



(13)

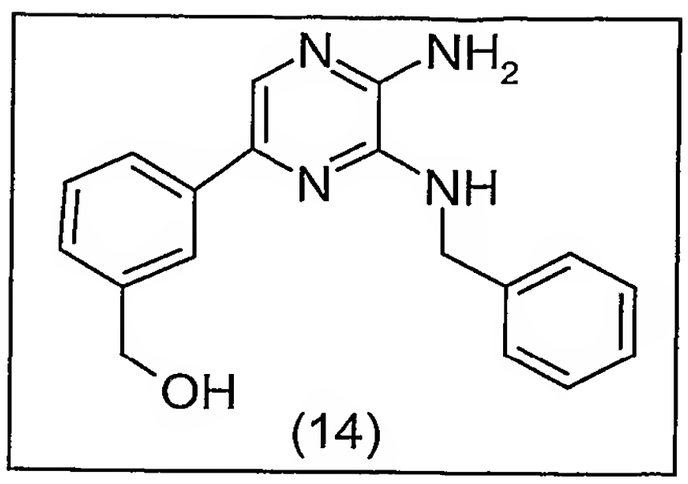
A mixture of 2-amino-3, 5-dibromopyrazine (4 mmol, 1eq.), aniline (4.4 mmol, 1.1 eq.) and K_2CO_3 (4.4 mmol, 1.1 eq.) in DMF (1ml) was placed in the Smith Creator and heated at 170°C for 30 minutes. The highly viscous

black solid was diluted with ethyl acetate filtered through a short pad of silica. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate and washed with water then brine. The ethyl acetate was removed under reduced pressure and the crude red oil was purified by column chromatography (50% hexane: ethyl acetate) to give the product as a green solid (0.28g, 15%); ^{1}H NMR ($CDCl_3$): δ^H 7.65 (s, 1H, PyzH), 7.22-7.19 (m, 1H, ArH), 6.79-6.71 (m, 2H, ArH), 6.07 (brs, 1H, NH), 4.37 (brs, 2H, NH_2), 3.81 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3); MS (APCI) m/z: 309 & 311 isotopes, (100%, $[M+H]^+$); HPLC 92%.

General procedure for the synthesis of compounds of formula (II).

To a solution of compound of formula (C) in degassed DMF (0.3mmol, 1 eq., 0.5ml) was added a solution of boronic acid in DMF (0.36mmol, 1.2 eq., 0.6ml) and 1.5M Na_2CO_3 (degassed aq.) solution (0.75mmol, 2.5 eq., 0.5ml). A solution of palladium (II) acetate (0.015 mmol, 0.05 eq., 168mg) and triphenylphosphine (0.045 mmol, 0.15 eq., 588mg) in degassed 1,4-dioxane (15ml) was freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml, yellow suspension) was then added to the reaction vessel under a nitrogen atmosphere and the contents were heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative reverse phase HPLC:

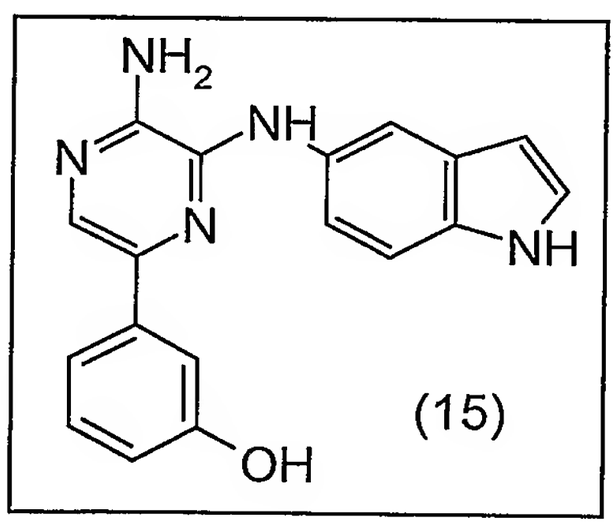
Typical example of compound of formula (II), as described in general reaction scheme; *{3-[5-amino-6-(benzylamino)pyrazine-2-yl]phenyl}methanol* ***(14)***.



(14)

Yield 10.4mg, 11%; ^{1}H NMR (DMSO): δ^H 8.52 (s, 1H, PyzH), 7.91 (brs, 1H, ArH), 7.83 (d, J=7.5Hz, 1H, ArH), 7.69 (brs, 1H, ArH), 7.63 (d, J=7.5Hz, 1H, ArH), 7.47 (t, J=7.5Hz, 1H, ArH), 6.29 (brs, exc., 2H, NH_2), 5.26-5.24 (m, exc., 2H, NH+OH), 4.57-4.52 (m, 4H, CH_2x2); MS (ES) m/z: 308 (100%, $[M+H]^+$); HPLC 100%.

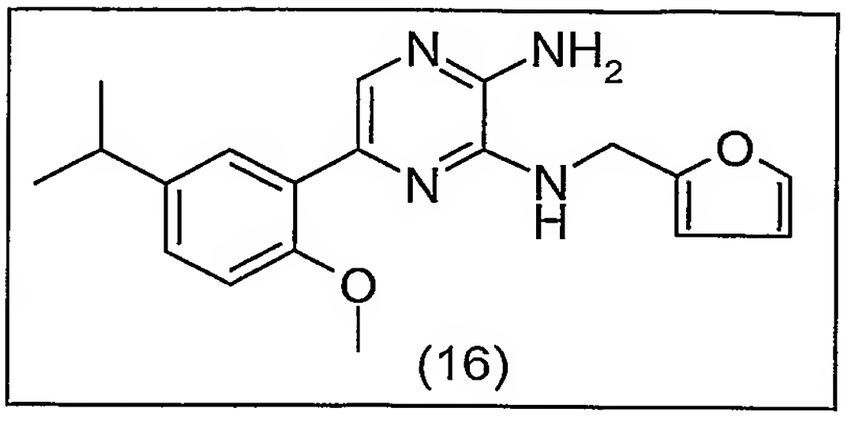
Typical example of compound of formula (II), as described in general reaction scheme; *3-[5-amino-6-(1H-indol-5-ylamino)pyrazin-2-yl]phenol* ***(15)***.



(15)

Yield 33.6mg, 35%; ^{1}H NMR (DMSO): δ^H 10.95 (brs, exc., 1H, indolNH), 9.37 (brs, exc., 1H, OH), 8.06 (brs, 2H, NH+ ArH), 7.82 (s, 1H, ArH), 7.42-7.12 (m, 6H, ArH), 6.65 (d, J=8Hz, 1H, Hα-indol), 6.38 (brs, 3H, NH_2+Hβ-indol); MS (ES) m/z: 318 (100%, $[M+H]^+$); HPLC 100%.

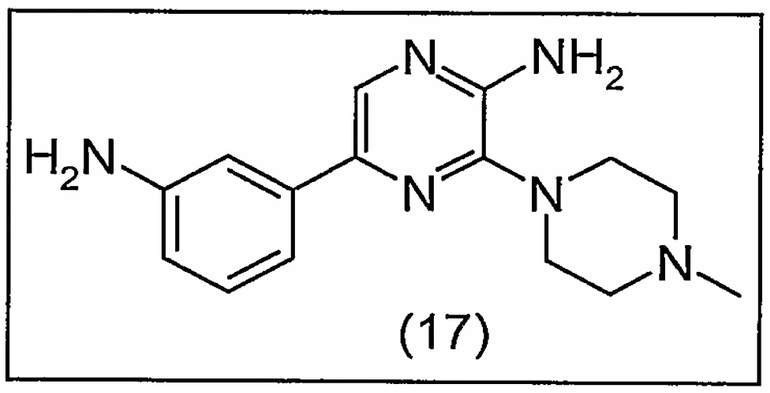
Typical example of compound of formula (II), as described in general reaction scheme; *N^3-(2-furylmethyl)-5-(5-isopropyl-2-methoxyphenyl)pyrazine-2,3-diamine* ***(16)***.



(16)

Yield 47.4mg, 46%; ^{1}H NMR (DMSO): δ^H 7.85 (s, 1H, PyzH), 7.70 (d, J=2.5Hz, 1H, ArH), 7.56 (dd, J=2Hz&1Hz, 1H, Fur-H), 7.07 (dd, J=8.5Hz&2.5Hz, 1H, ArH), 6.94(d, J=8.5Hz, 1H, ArH), 6.66 (t, exc., J=5Hz, 1H, NH), 6.38 (dd, J=3Hz&2Hz, 1H, Fur-H), 6.30-6.28 (m, 1H, Fur-H), 6.08 (brs, exc., 2H, NH_2), 4.57 (d, J=5Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 2.90-2.79 (m, 1H, CH), 1.19 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); MS (ES) m/z: 339 (100%, $[M+H]^+$); HPLC 100%.

Typical example of compound of formula (II), as described in general reaction scheme; *5-(3-aminophenyl)-3-(4-methylpiperazin-1-yl)pyrazin-2-amine* ***(17)***.



(17)

Yield 56.1mg, 66%; ^{1}H NMR (DMSO): δ^H 8.02 (s, 1H, PyzH), 7.12-7.11 (m, 1H, ArH), 7.04-6.98 (m, 1H, ArH), 6.49-6.45 (m, 1H, ArH), 5.95 (brs, exc., 2H, NH_2), 5.07 (brs, exc., 2H, NH_2), 3.12-2.98(m, 4H, 2xCH_2), 2.52-2.47 (m, 4H, 2xCH_2), 2.22 (s, 3H, CH_3); MS (ES) m/z: 285 (100%, $[M+H]^+$); HPLC 100%.

Purification Conditions

All compounds have a minimum purity level ≥ 80% as measured by LCMS at 254 nm.

The columns used for the preparative HPLC purification of the various scaffolds are outlined in Table 1:

Table 1

Scaffold	Column
All compounds	Waters Xterra® Prep MS C18 5μm 19 x 100mm

The gradient used for the preparative HPLC purification of all compounds was 95% water (10mmol NH_3HCO_3) 5% acetonitrile for 1 min to 5% water (10mmol NH_3HCO_3) / 95% acetonitrile over 8.0 min then held at 5% water (10mmol NH_3HCO_3) / 95% acetonitrile for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

A flow rate of 25 ml/min was used.

The conditions used for the analytical HPLC analysis following preparative HPLC purification are outlined in Table 2:

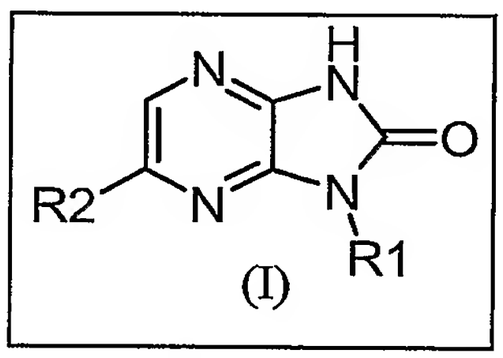
Table 2

Conditions	Detection
Column: Waters Xterra® Prep MS C18 5μm 4.6 x 100mm. **Gradient**: 95% water (10 mM NH_3HCO_3) / 5% ACN for 0.5 min then 95% water (10 mM NH_3HCO_3) / 5% ACN to 2% water (10 mM NH_3HCO_3) / 98% ACN over 3.5 min. Held at 2% water (10 mM NH_3HCO_3) / 98% ACN for 0.5 min. The solvent mixture is then returned to the initial conditions over 0.1 min and the system allowed to re-equilibrate for 0.2 min. **Flow rate:** 2.0 ml/min. **Temperature:** 30 °C. **Injection volume:** 5 μm partial loop.	UV detection at 254 nm (diode array range 210-280nm). **Electrospray ionisation**: Cone voltage: 30 V. Cone temperature: 20 °C. Source temperature 150 °C. RF lens voltage: 0.0 V. Ion energy: 0.5 eV. Multiplier: 650 V.

LIBRARY SFK20

SFK20 is designed to have a broad focus on tyrosine and serine/threonine kinases that recognise typical bicyclic heterocyclic ligands for the ATP binding site. The central design of the library is based on novel applications of the imidazopyrazine-2-one scaffold which has been docked into the ATP-binding region of a variety of kinases including CDK2, FGFr1, PKA, Hck and Erk2. The library has been designed to mimic the characteristic double H-bonding system seen between ATP and the protein kinase backbone by utilising the embedded amide motif. Two major docking modes are observed: In mode 1, the amide donor-acceptor pair provides the key backbone interactions (for example, H-bonds to Phe^{82} and Glu^{81} in CDK2): In mode 2, a pyrazine nitrogen acts as acceptor and the amide NH as donor, with a third H-bond possible to the amide CO.

The invention provides a compound library comprising or consisting of a set of structurally related compounds of the general formula (I).

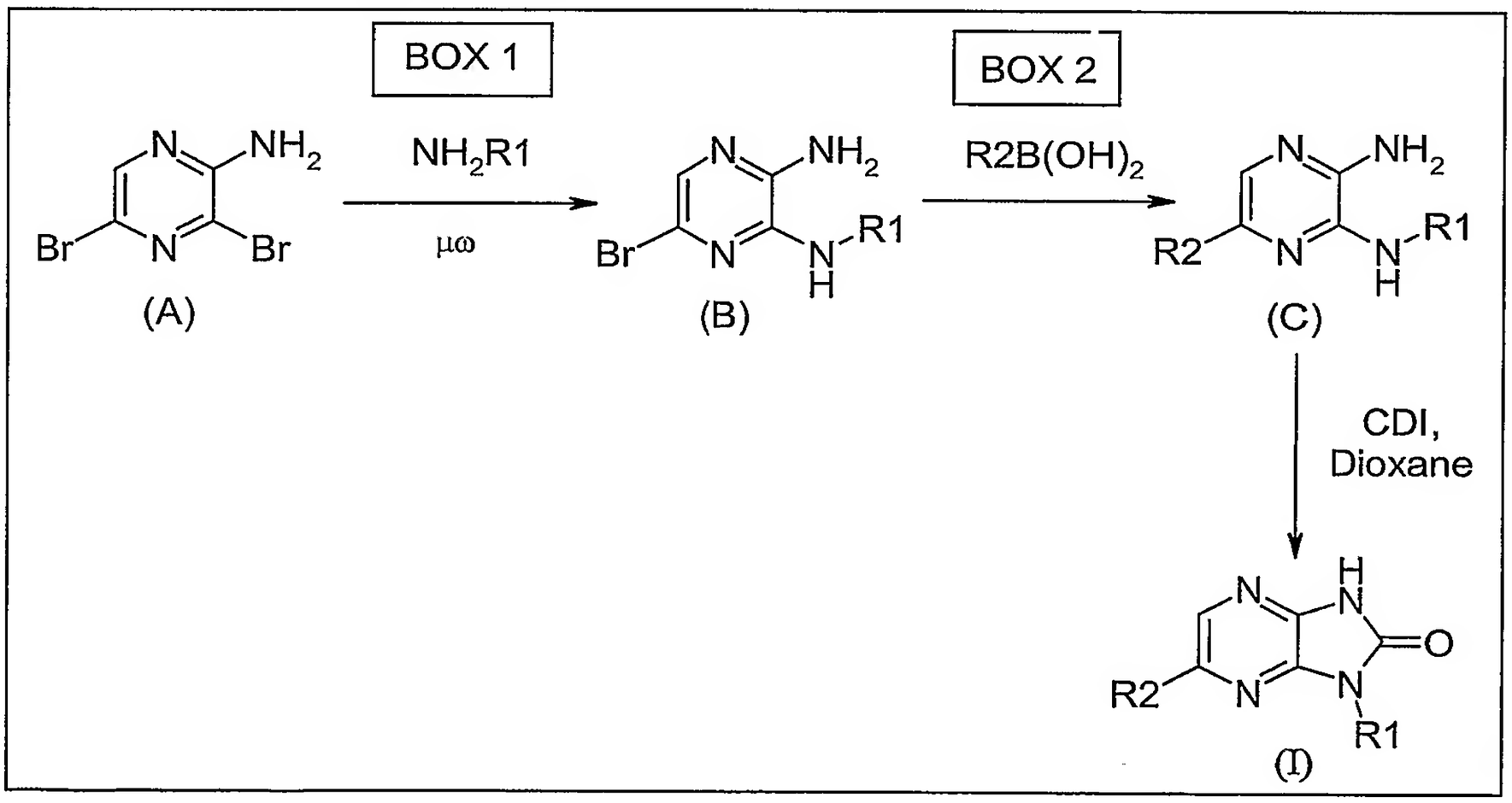


(I)

Wherein R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may

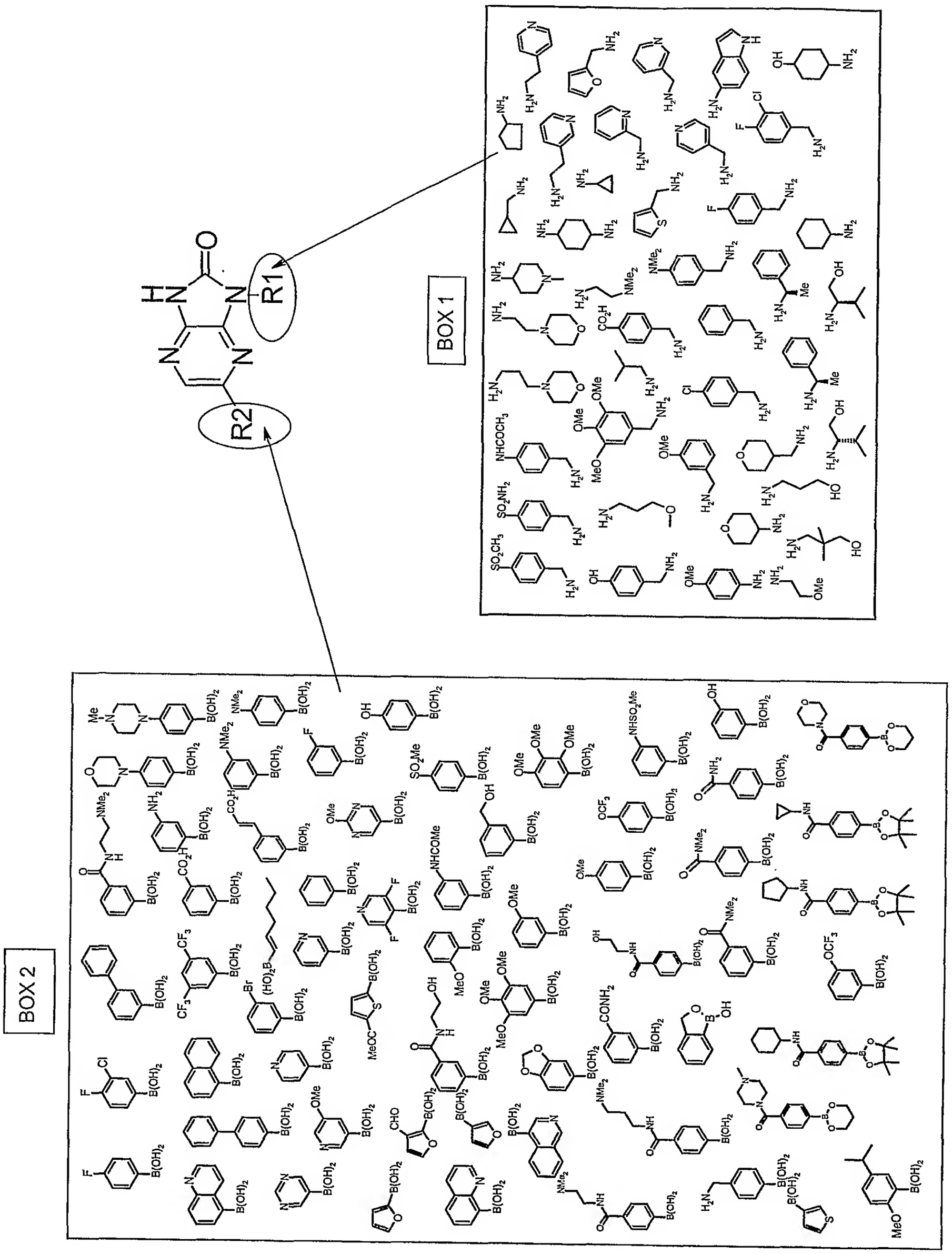
contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and R2 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

Scheme for synthesising compounds of formula (I)



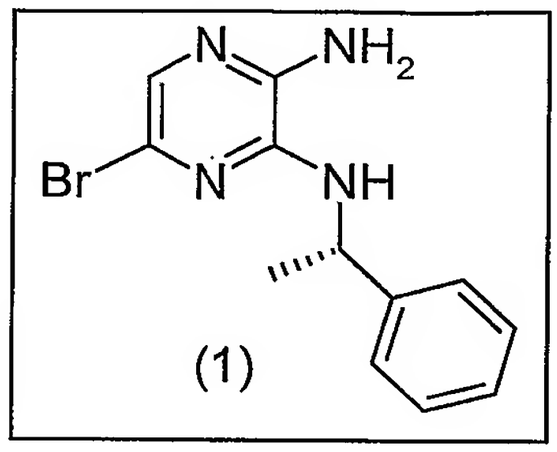
2-Amino-3, 5–dibromopyrazine (A) can be aminated with the amines described in Box 1. The resultant compounds (B) can then be reacted with

the boronic acids described in Box 2. Cyclisation of the intermediates (C) yields the desired targets (I).


BOX 1
BOX 2
R1
R2

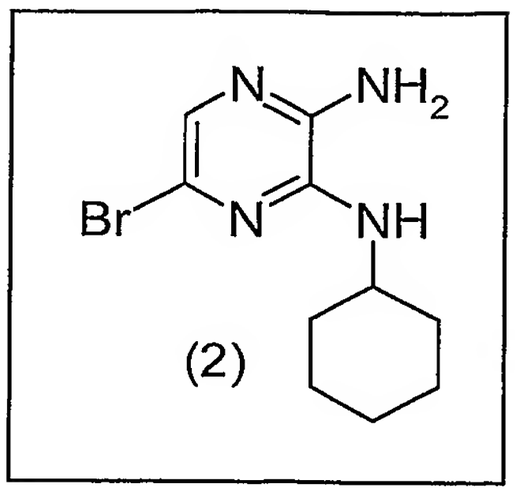
General procedures

Typical example of compound of formula (B), as described in the general reaction scheme; *N^3-[(1R)-1-phenylethyl]-5-bromo-2,3-pyrazine diamine* ***(1)***.



A mixture of 2-amino-3, 5-dibromopyrazine (60 mmol, 1eq.), (S)-(-)-(alpha)-methylbenzylamine (66 mmol, 1.1 eq.) and DIPEA (66 mmol, 1.1 eq.) in ethanol (15ml) was placed in the CEM Discover and heated and stirred at 180^{0}C for 90 mins. The contents of the tubes were then transferred to a round-bottomed flask and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine and then filtered through a pad of silica using ethyl acetate as the eluant. The solvent was evaporated under reduced pressure and the crude residue was slurried in hexane. The solidified product was filtered, washed with hexane and dried to give the product as a brown solid (6.82g, 77%); ^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 7.64-7.30 (m, 4H, ArH), 7.23-7.19 (m, 1H, ArH), 7.18 (s, 1H, PyraH), 6.84 (d, 1H, J 7.50 Hz, NH), 6.29 (brs, 2H, NH_2), 5.13-5.01 (m, 1H, CH), 1.4 (d, 3H, J 7.50Hz, CH_3); MS (AP+, $[M+H]^+$) m/z: 293 & 295 (M^{+1}), 334 & 336 ($M+CH_3CN$); HPLC 95%.

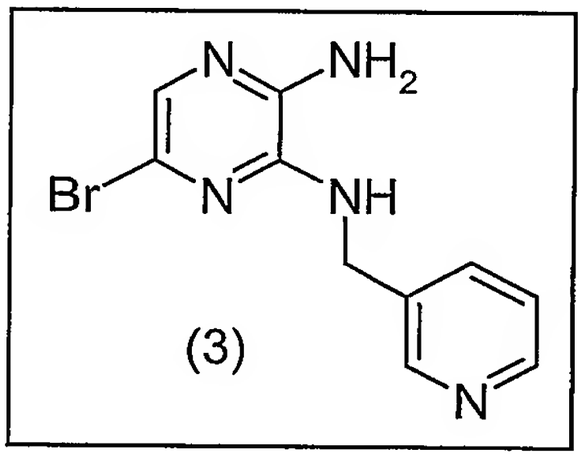
Typical example of compound of formula (B), as described in the general reaction scheme; *N^3-cyclohexyl-5-bromo-2, 3-pyrazine diamine* ***(2)***.



(2)

Yield (5g, 77%); ^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 7.11 (s, 1H, PyraH), 6.23 (brs, 1H, NH), 6.17 (brs, 2H, NH_2), 3.71-3.66 (m, 1H, NCH), 1.97-1.88 (m, 2H, CH_2), 1.73-1.56 (m, 2H, CH_2), 1.37-1.28 (m, 1H, CH), 1.23-1.11 (m, 5H, CH_2x2 & CH); MS (AP+, $[M+H]^+$) m/z: 271 & 273 (M^{+1}), 312 & 314 ($M+CH_3CN$); HPLC 100%.

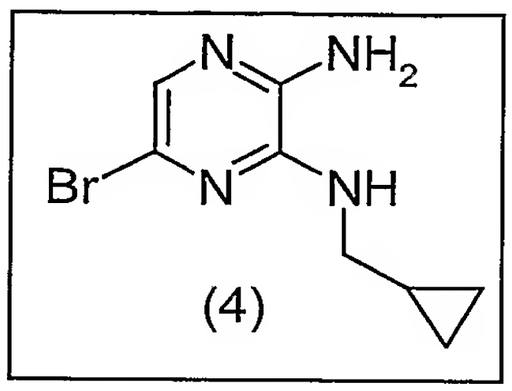
Typical example of compound of formula (B), as described in the general reaction scheme; *N^3-(3-pyridylmethyl)-5-bromo-2, 3-pyrazine diamine* ***(3)***.



(3)

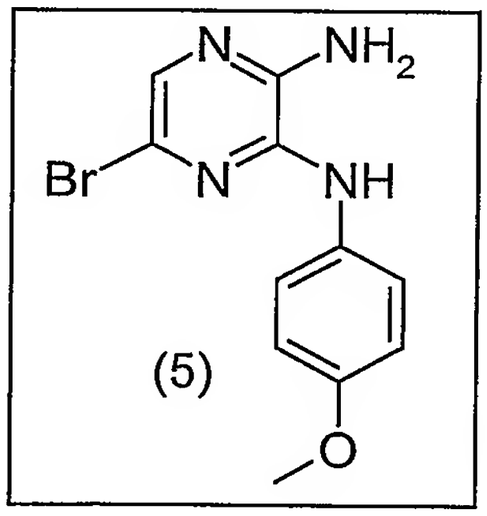
Yield (8.60g, 73%);^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 8.51 (d, 1H, J 5Hz, PyrH), 7.74 (t, 1H, J 7.50Hz, PyrH), 7.31 (d, 1H, J 7.50Hz, PyrH), 7.26 (t, 1H, J 5Hz, NH), 7.19 (s, 1H, PyraH), 7.18-7.15 (m, 1H, PyrH), 6.27 (s, 2H, NH_2), 4.58 (d, 2H, J 5Hz, CH_2); MS (AP+, $[M+H]^+$) m/z: 280 & 282 (M^{+1}); HPLC 99%.

Typical example of compound of formula (B), as described in the general reaction scheme; *N^3-cyclopropylmethyl-5-bromo-2, 3-pyrazine diamine* ***(4)***.



Yield (11g, 84%); ^{1}HNMR (250MHz, DMSO$^d{}_6$): δ*ppm*, 6.91 (s, 1H, PyraH), 6.40 (t, 1H, J 5Hz, NH), 5.98 (s, 2H, NH_2), 2.88 (t, 2H, J 5Hz, CH_2), 0.81-0.74 (m, 1H, CH), 029-0.25 (m, 2H, CH_2), 0.22-0.17 (m, 2H, CH_2); MS (ES+, $[M+H]^+$) m/z: 243 & 245 (M^{+1}), 284 & 286 (M+ CH_3CN); HPLC 98%.

Typical example of compound of formula (B), as described in the general reaction scheme; *N^3-(3-methoxyphenyl)-5-bromo-2, 3-pyrazine diamine* ***(5)***.



A mixture of 2-amino-3, 5-dibromopyrazine (4 mmol, 1eq.), 4-methoxyaniline (4.4 mmol, 1.1 eq.) and K_2CO_3 (4.4 mmol, 1.1 eq.) in DMF (1ml) was placed in the Smith Creator and heated with stirring for 30 mins at 160^{0}C. The contents of the tubes (highly viscous black semi-solid) were dissolved in ethyl acetate and combined. The mixture was then filtered

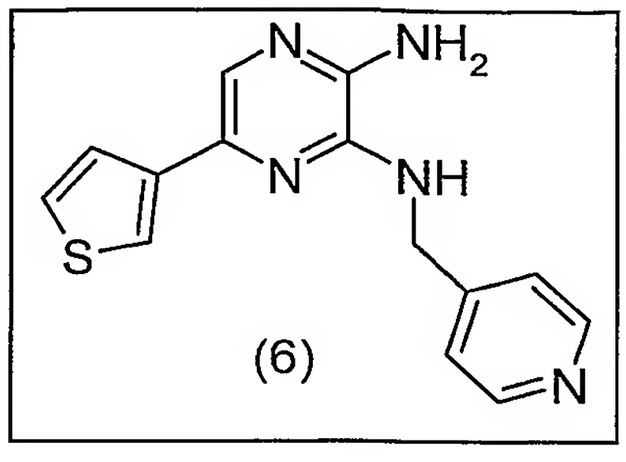
through a short pad of silica and the filtrate was concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with water and brine. The ethyl acetate was removed under reduced pressure and the crude organic residue was further purified by a silica column chromatography using ethyl acetate/ hexane (1:3 and then 1:1). After the evaporation of the fractions that contained the product, the residue was crystallised by triturating in hexane/ 20% DCM. The solid was filtered, washed with hexane/ 20% DCM and dried to give the title product as a brown solid (4.37g, 19%); ^{1}HNMR (250MHz, $CDCl_3$) δ*ppm*: 8.52 (s,1H, NH), 7.58 (d, 2H, J 9Hz, ArH), 7.36 (s, 1H, PyraH), 6.90 (d, 2H, J 9Hz, ArH), 6.56 (s, 2H, NH_2), 3.69(s, 3H,CH_3); MS (ES+, $[M+H]^+$) m/z: 295 &297 (M^{+1}); HPLC 89 %.

General procedure for the synthesis of compounds of formula (C)

The Suzuki reactions were carried out in STEM tubes using a 96 position heater shaker unit.

To a solution of the required intermediates (B) in degassed DMF (0.3mmol, 1 eq., 0.5ml) was added a solution of boronic acid (Box 2) in DMF (0.36mmol, 1.2 eq., 0.6ml) and 1.5M Na_2CO_3 (degassed aq.) solution (0.75mmol, 2.5 eq., 0.5ml). A solution of palladium (II) acetate (0.015 mmol, 0.05 eq., 168mg) and triphenylphosphine (0.045 mmol, 0.15 eq., 588mg) in degassed 1,4-dioxane (15ml) was freshly prepared and placed in a sonication bath for 2min. The palladium catalyst (0.3ml, yellow suspension) was then added to the reaction vessel under a nitrogen atmosphere and the contents were heated at 80°C with agitation for 16h. The reaction mixtures were filtered and purified by preparative reverse phase HPLC.

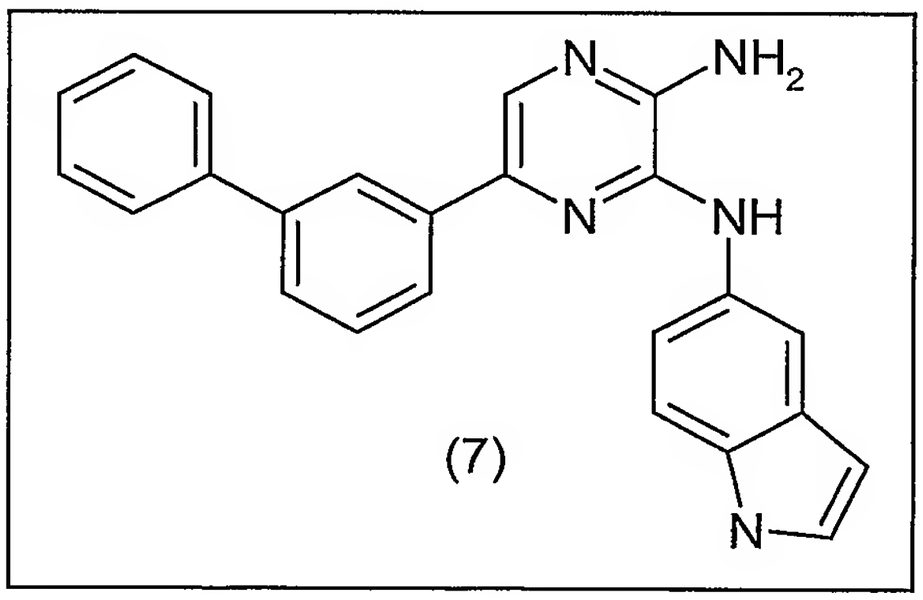
Typical example of compound of formula (C), as described in the general reaction scheme; *N^3-(4-pyridylmethyl)-5-(3-thienyl)-2, 3-pyrazine diamine* ***(6)***.



(6)

Yield (4.5 mg, 5%); ^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 8.32 (d, 2H, J 5Hz, PyrH), 7.50 (s, 1H, PyraH), 7.44 (s, 1H, ThiopH), 7.35-7.30 (m, 2H, ThiopH), 7.26 (d, 2H, J 5Hz, PyrH), 6.82 (t, 1H, J 5Hz, NH), 5.98 (brs, 2H, NH_2), 4.47 (d, 2H, J 5Hz, CH_2); MS (ES+, $[M+H]^+$) m/z: 284 (M^{+1}); HPLC 99.60%.

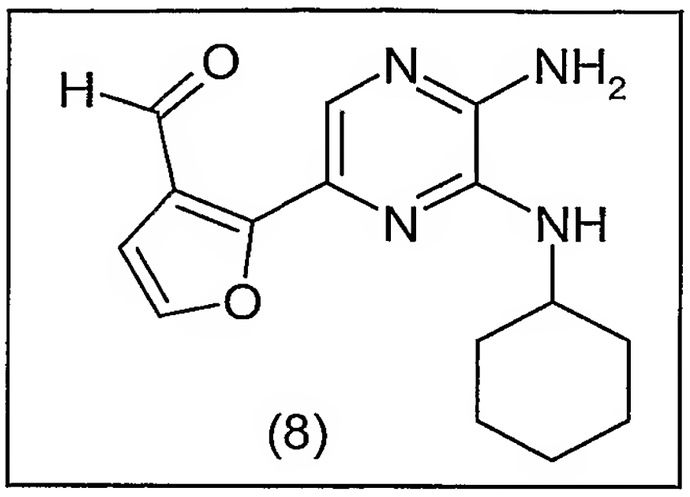
Typical example of compound of formula (C), as described in the general reaction scheme; *N^3-(1H-5-indolyl-5-(3-biphenyl)-2, 3-pyrazine diamine* ***(7)***.



(7)

Yield (3.1 mg, 3%); ^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 11.20 (brs, 1H, IndH), 8.42 (d, 1H, J 9Hz, IndH), 8.30 (s, 1H, IndH), 8.20 (s, 1H, PyraH), 8.05 (d, 1H, J 5Hz, ArH), 7.81-7.42 (m, 11H, ArH/IndH), 6.66 (s, 2H, NH_2), 6.53 (brs, 1H, NH); MS (ES+, $[M+H]^+$) m/z: 378 (M^{+1}); HPLC 81%.

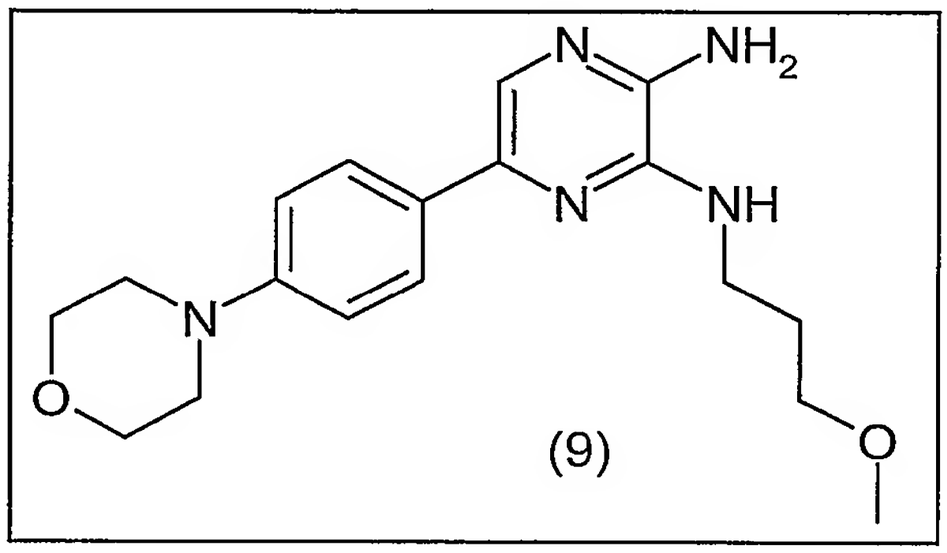
Typical example of compound of formula (C), as described in the general reaction scheme; *2-[5-amino-6-(cyclohexylamine)-2-pyrazinyl]-3-furaldehyde* ***(8)***.



(8)

Yield (4.8 mg, 5.50%); ^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 10.3 (s, 1H, CHO), 7.75 (s, 1H, PyraH), 7.67 (d, 1H, J 2.5Hz, FurH), 6.78 (d, 1H, J 2.5Hz, FurH), 6.72 (s, 2H, NH_2), 6.35 (d, 1H, J 5Hz, NH), 3.67-3.55 (m, 1H, NCH), 2.06-1.89 (m, 2H, CH_2), 1.77-1.61 (m, 3H, CH_2), 1.47-1.15 (m, 5H, CH_2x2 & CH); MS (ES+, $[M+H]^+$) m/z: 287 (M^{+1}); HPLC 100%.

Typical example of compound of formula (C), as described in the general reaction scheme; *N^3-(3-methoxypropyl)-5-(4-morpholinophenyl)-2, 3-pyrazine diamine* ***(9)***.



(9)

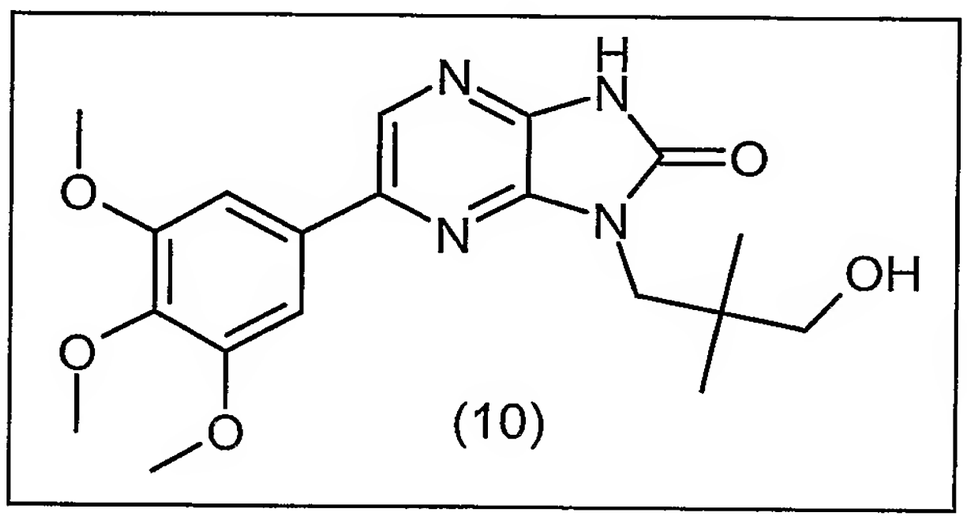
Yield (4.4 mg, 4.27%); ^{1}HNMR (250MHz, DMSO$^d_6$): δ*ppm*, 7.74 (d, 2H, J 7.5Hz, ArH), 7.62 (s, 1H, PyraH), 6.95 (d, 2H, J 7.5Hz, ArH), 6.17 (t, 1H, J 5Hz, NH), 5.93 (s, 2H, NH_2), 3.71-3.75 (m, 4H, CH_2), 3.47-3.38 (m, 4H,

NCH_2), 3.29 (s, 3H, OCH_3), 3.12-3.08 (m, 4H, CH_2), 1.85-1.77 (m, 2H, CH_2); MS (ES+, $[M+H]^+$) m/z: 344 (M^{+1}); HPLC 100%.

General procedure for the synthesis of compounds of formula (I)

To a solution of the required intermediates (C) (71.2 mg, 0.196 mmol) in anhydrous 1,4-dioxane (1ml) was added a solution of 1,1'-carbonyldiimidazole (2.5eq.) in anhydrous 1,4-dioxane (0.5ml). The reactions were heated at 65°c, overnight after which they were transferred into a 48 well plate and purified by preparative reverse phase HPLC.

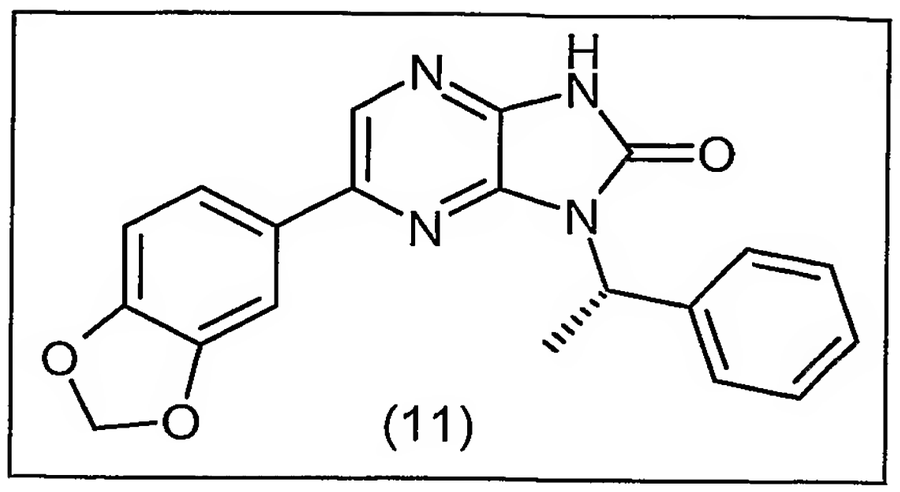
Typical example of compound of formula (I), as described in the general reaction scheme; *1-[3-hydroxy-2, 2-dimethylpropyl)-6-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydro-1H-imidazo[4, 5-b]pyrazin-2-one* ***(10)***.



(10)

Yield (2 mg, 2.6%); ^{1}HNMR (250MHz, $DMSO^d_6$): δ*ppm*, 12.10 (s, 1H, NH), 8.55 (s, 1H, PyraH), 7.34 (s, 2H, ArH), 4.72 (brs, 1H, OH), 3.85 (s, 6H, OMex2), 3.74 (s, 2H, CH_2O), 3.68 (s, 3H, OMe), 3.23 (s, 2H, NCH_2), 0.91 (s, 6H, CH_3x2) ; MS (ES+, $[M+H]^+$) m/z: 389 (M^{+1}); HPLC 100%.

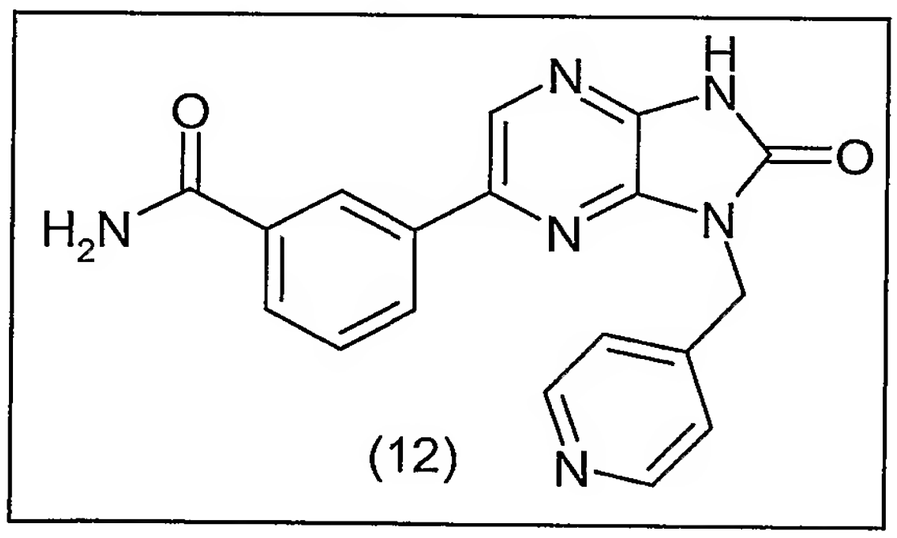
Typical example of compound of formula (I), as described in the general reaction scheme; *6-(1, 3-benzodioxol-5-yl)-1-[(1R)-1-phenylethyl])-2,3-dihydro-1H-imidazo [4, 5-b]pyrazin-2-one* ***(11)***.



(11)

Yield (4.4 mg, 3%); ^{1}HNMR (250MHz, DMSO$^d_6$): δppm, 8.17 (s, 1H, PyraH), 7.30-7.22 (m, 4H, ArH), 7.13-7.01(m, 3H, ArH), 6.77 (d, 1H, J 7.5Hz, ArH), 5.87 (s, 2H, OCH_2), 5.47 (q, 1H, J 7.5Hz, CH), 1.74 (d, 3H, CH_3); MS (ES+, $[M+H]^+$) m/z: 361 (M^{+1}), 402 (M^++ CH_3CN); HPLC 100%.

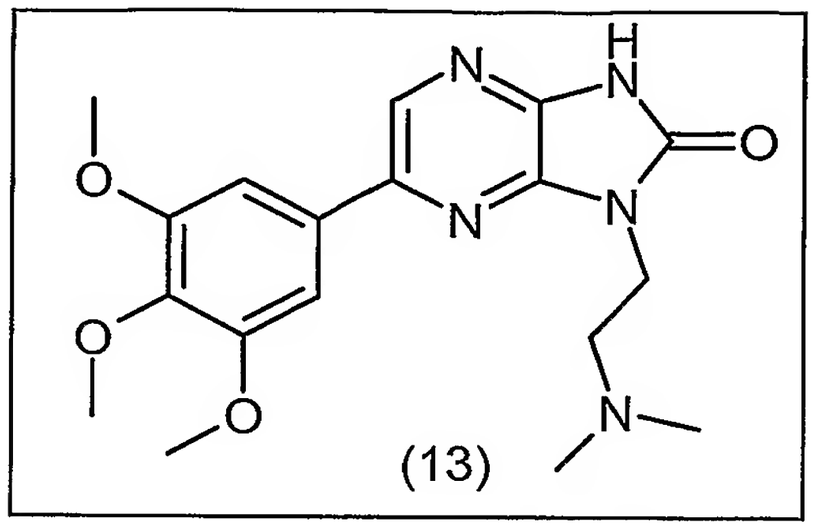
Typical example of compound of formula (I), as described in the general reaction scheme; *3-[2-oxo-3-(4-pyridylmethyl)-2, 3-dihydro-1H-imidazo[4, 5-b]pyrazin-5-yl]benz-amide* ***(12)***.



(12)

Yield (5.6 mg, 26.70%); ^{1}HNMR (250MHz, DMSO$^d_6$): δppm, 8.85 (s, 1H, PyraH), 8.52 (d, 2H, J 5Hz, PyrH), 8.44 (s, 1H, ArH), 8.08 (brs, 2H, NH_2), 7.86 (d, 1H, J 7.5Hz, ArH), 7.55-7.46 (m, 2H, ArH), 7.35 (d, 2H, J 5Hz, PyrH), 5.11 (s, 2H, CH_2); MS (ES+, $[M+H]^+$) m/z: 347 (M^{+1}); HPLC 100%.

Typical example of compound of formula (I), as described in the general reaction scheme; *1-[2-(dimethylamino)ethyl]-6-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydro-1H-imidazo [4, 5-b]pyrazin-2-one* ***(13)***.



Yield (4.6 mg, 11.57%); ^{1}HNMR (250MHz, DMSO$^d_6$): δppm, 12.10 (brs, 1H, NH), 8.55 (s, 1H, PyraH), 7.31 (s, 2H, ArH), 3.97 (t, 2H, J 7.5Hz, CH_2), 3.84 (s, 6H, 2 x OCH_3) 3.68 (s, 3H, OCH_3), 2.60 ((t, 2H, J 7.5Hz, CH_2), 2.19 (s, 6H, $N(CH_3)_2$); MS (ES+, $[M+H]^+$) m/z: 374 (M^{+1}); HPLC 100%.

Purification Conditions

All compounds have a minimum purity level ≥ 80% as measured by LCMS at 254 nm.

The columns used for the preparative HPLC purification of the various scaffolds are outlined in Table 1:

Table 1

Scaffold	Column
All compounds	Varian Polaris 10μm C18-A 150 x 21.2mm

The gradient used for the preparative HPLC purification of all compounds was 95% water (10mmol NH_3HCO_3) 5% acetonitrile for 1 min to 5% water (10mmol NH_3HCO_3) / 95% acetonitrile over 8.0 min then held at 5% water (10mmol NH_3HCO_3) / 95% acetonitrile for 2.0 min. The solvent mixture was then returned to the initial conditions over 0.5 min.

A flow rate of 25 ml/min was used.

The conditions used for the analytical HPLC analysis following preparative HPLC purification are outlined in Table 2:

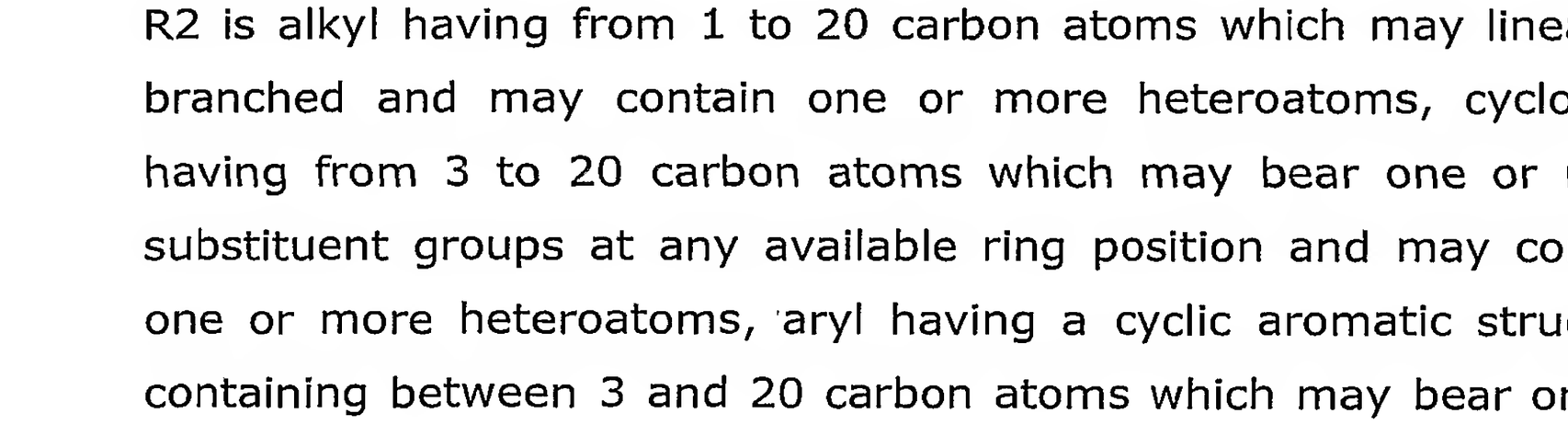
Table 2

Conditions	Detection
Column: Waters Xterra® Prep MS C18 5μm 4.6 x 100mm. **Gradient**: 95% water (10 mM NH_3HCO_3) / 5% ACN for 0.5 min then 95% water (10 mM NH_3HCO_3) / 5% ACN to 2% water (10 mM NH_3HCO_3) / 98% ACN over 3.5 min. Held at 2% water (10 mM NH_3HCO_3) / 98% ACN for 0.5 min. The solvent mixture is then returned to the initial conditions over 0.1 min and the system allowed to re-equilibrate for 0.2 min. **Flow rate:** 2.0 ml/min. **Temperature:** 30 °C. **Injection volume:** 5 μm partial loop.	UV detection at 254 nm (diode array range 210-280nm). **Electrospray ionisation**: Cone voltage: 30 V. Cone temperature: 20 °C. Source temperature 150 °C. RF lens voltage: 0.0 V. Ion energy: 0.5 eV. Multiplier: 650 V.

It will be appreciated by those skilled in the art that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognise apparent modifications and variations that may be made without departing from the spirit of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

CLAIMS

1. A library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II and/or formula III:



wherein,

R1 is hydrogen or R1 is joined with R2 to form the same ring system;

R4 is hydrogen;

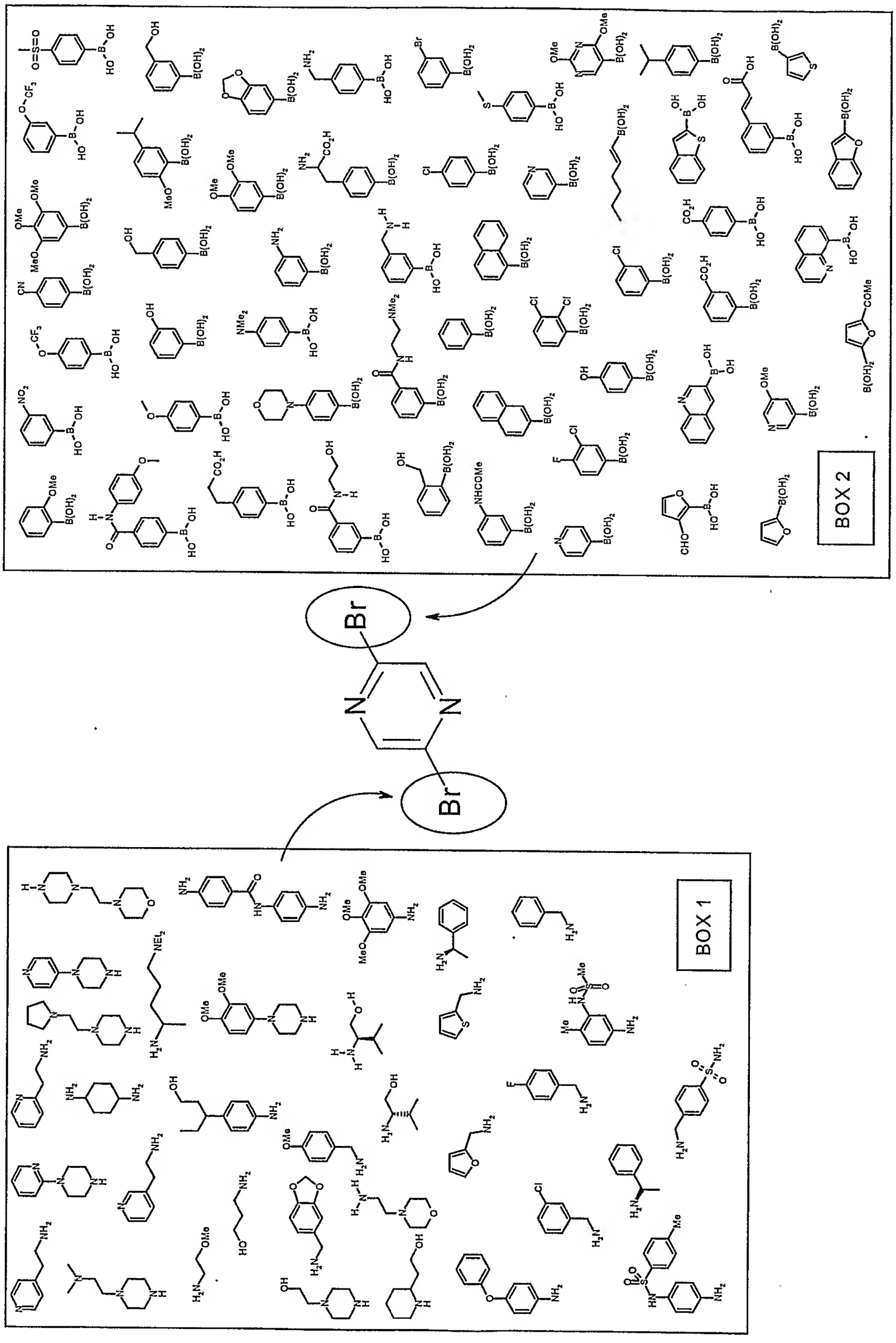
R2 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

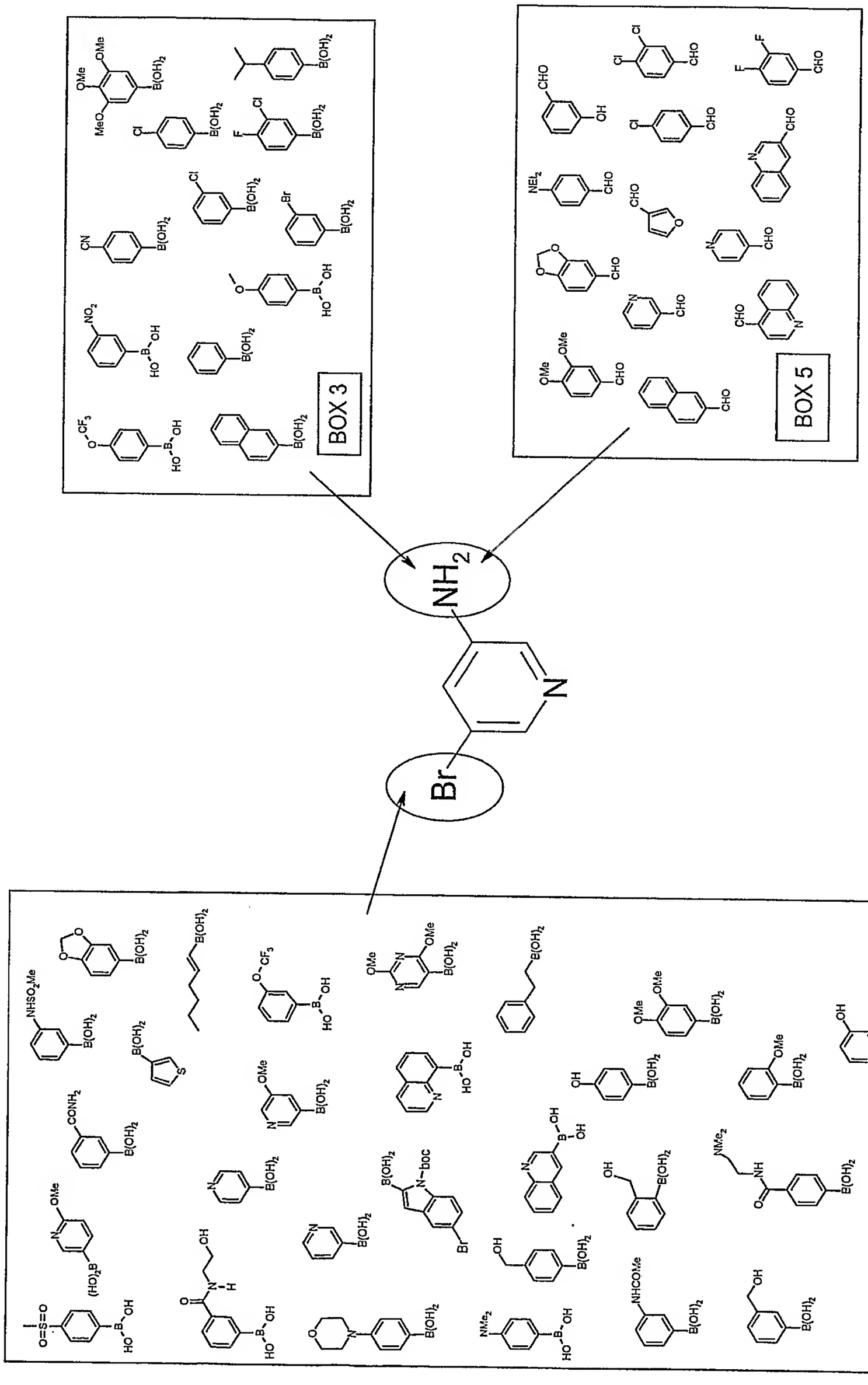
R3 and R6 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

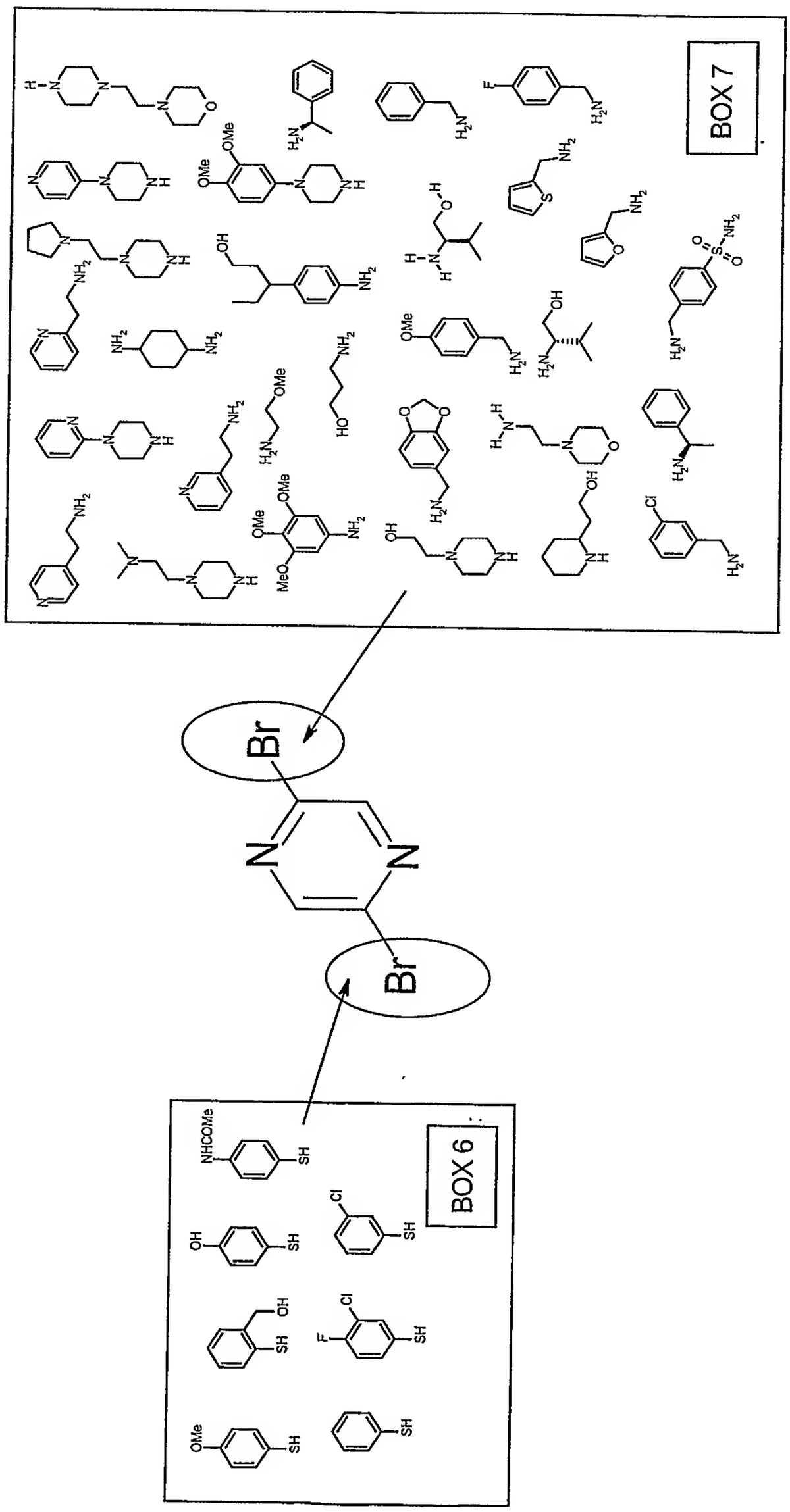
R5 is aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

R7 is aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position.

2. A library according to claim 1 which comprises or consists of a structurally related set of compounds, said library comprising compounds selected from the compounds shown by the following scatter diagrams:

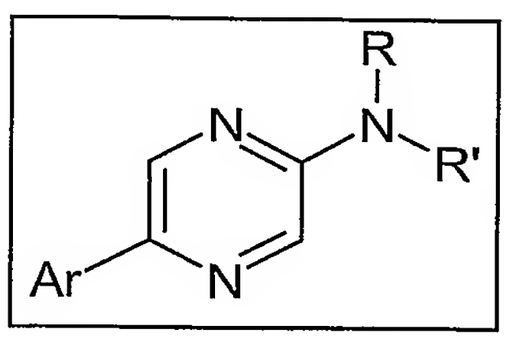

BOX 2
Br
Br
N
N
BOX 1


BOX 3
BOX 5
BOX 4
NH2
Br
N


BOX 7
BOX 6
Br
Br

3. A compound having a core chemical structure (scaffold) which is selected from:

i)



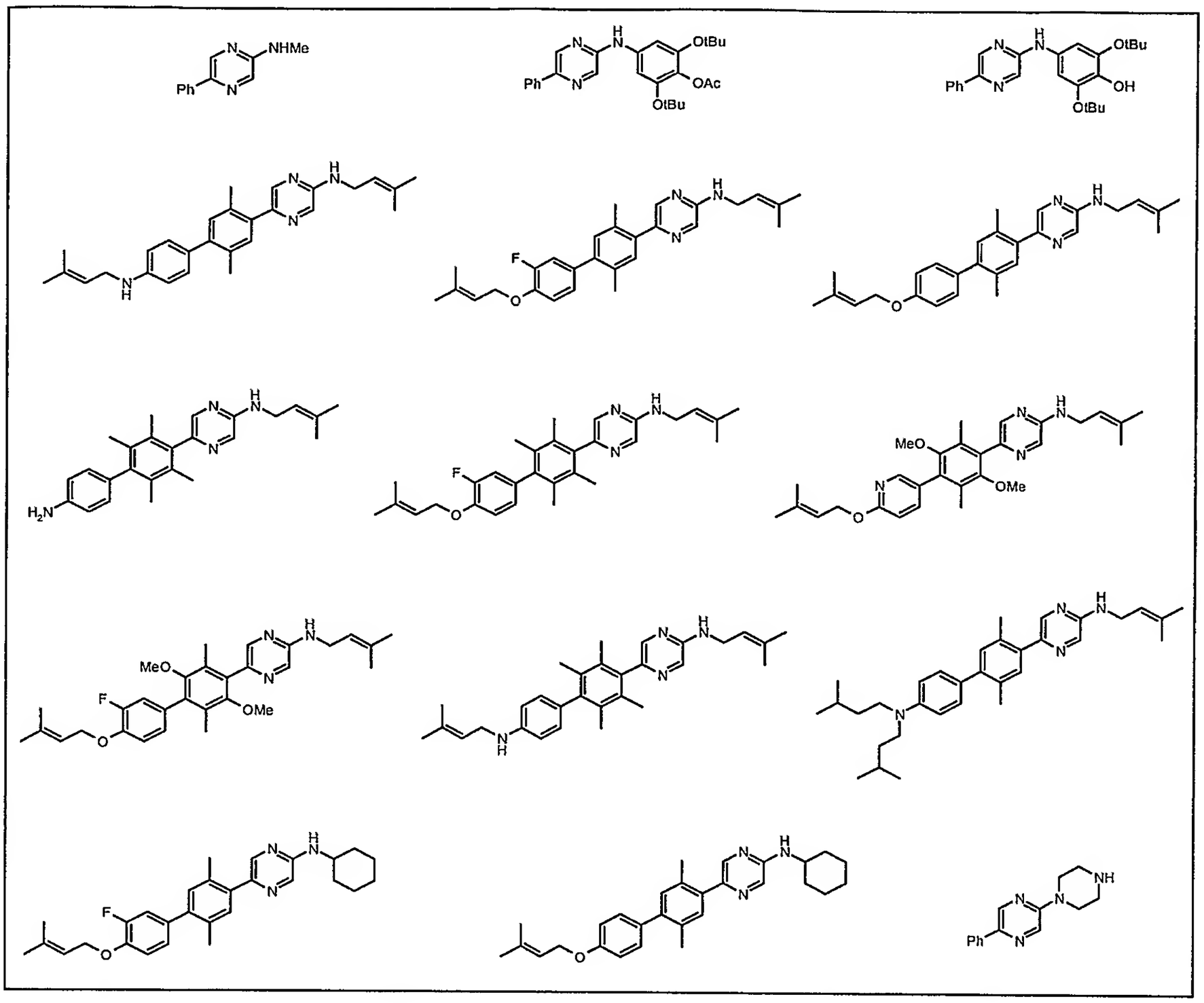
wherein

R is hydrogen or R is joined with R' to form the same ring system;

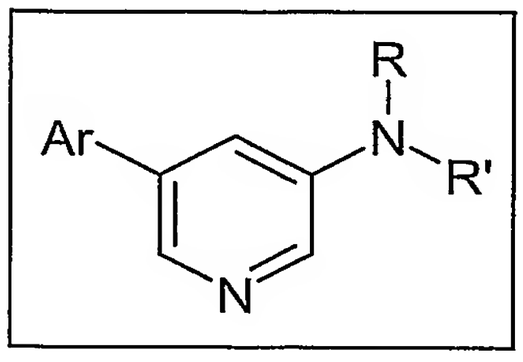
R' is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

Ar is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

excluding the following compounds:



ii)



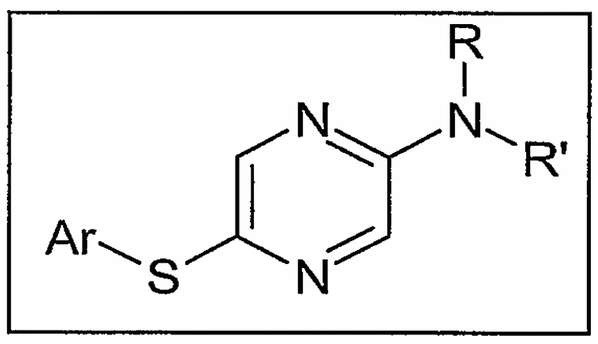
wherein

R is hydrogen;

R' is aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

Ar is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; or

iii)



wherein

R is hydrogen or R is joined with R' to form the same ring system;

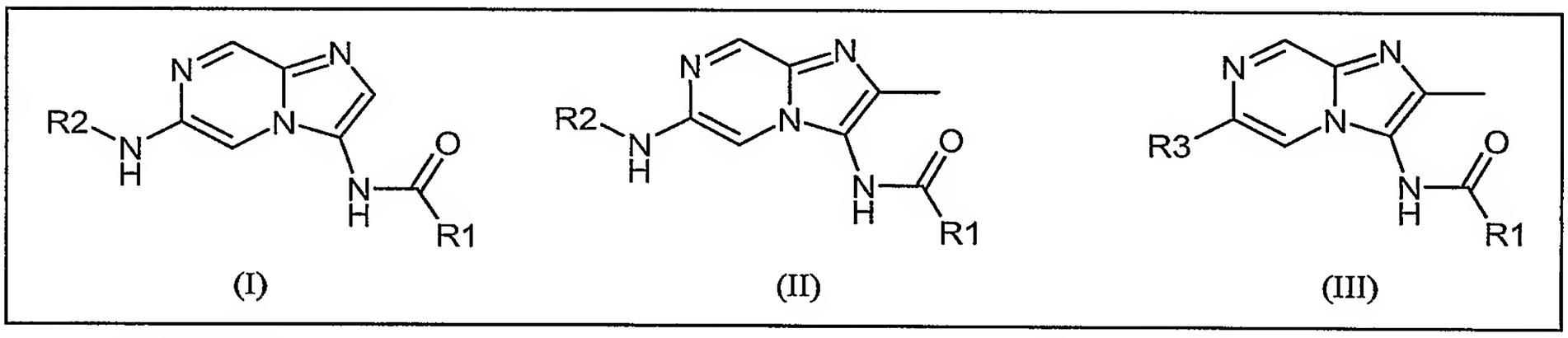
R' is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may

bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

Ar is aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position.

4. A compound according to claim 3 which is selected from the compounds represented within the library of claim 2.

5. A library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II and/or formula III:



wherein

R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position

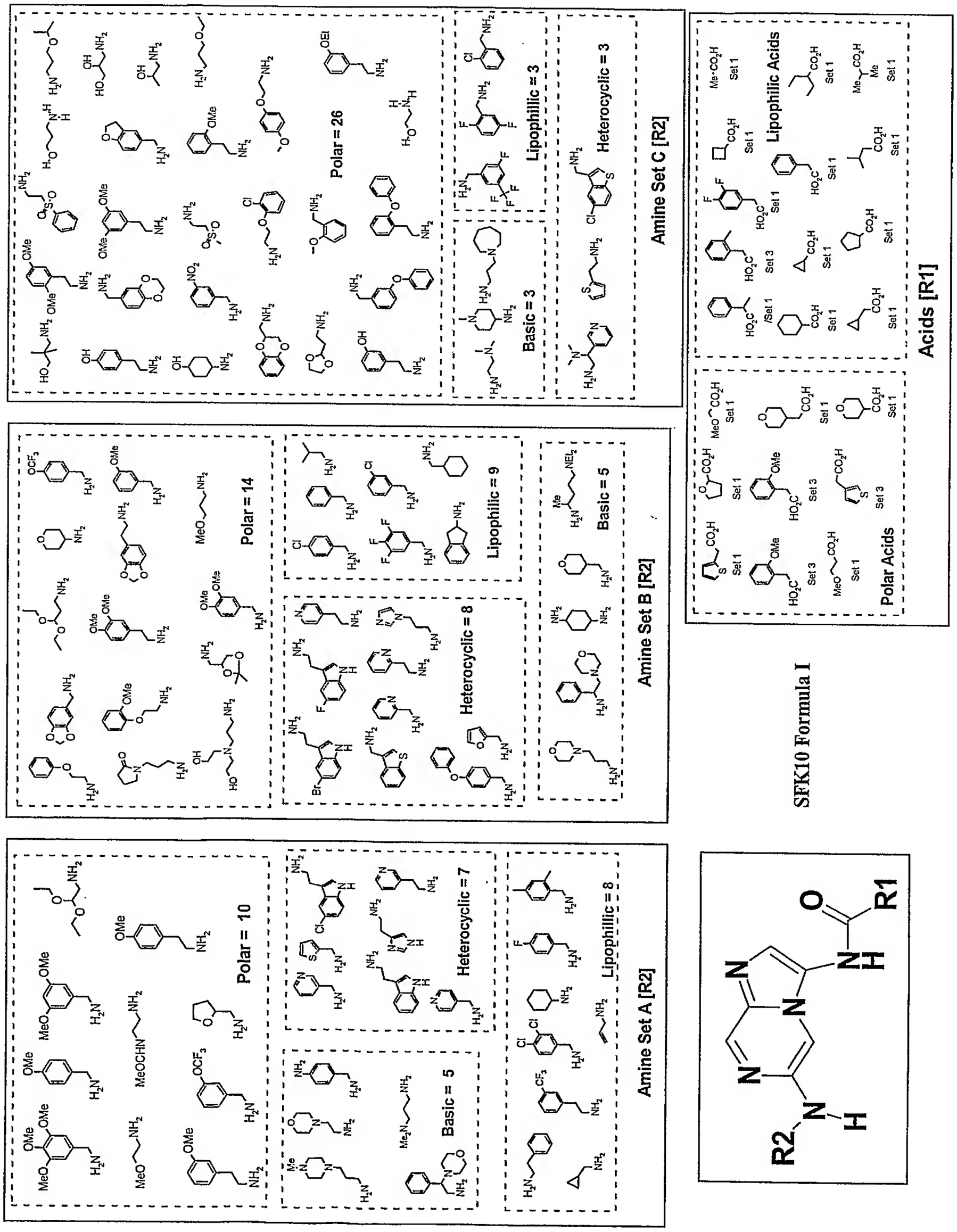
and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

R2 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

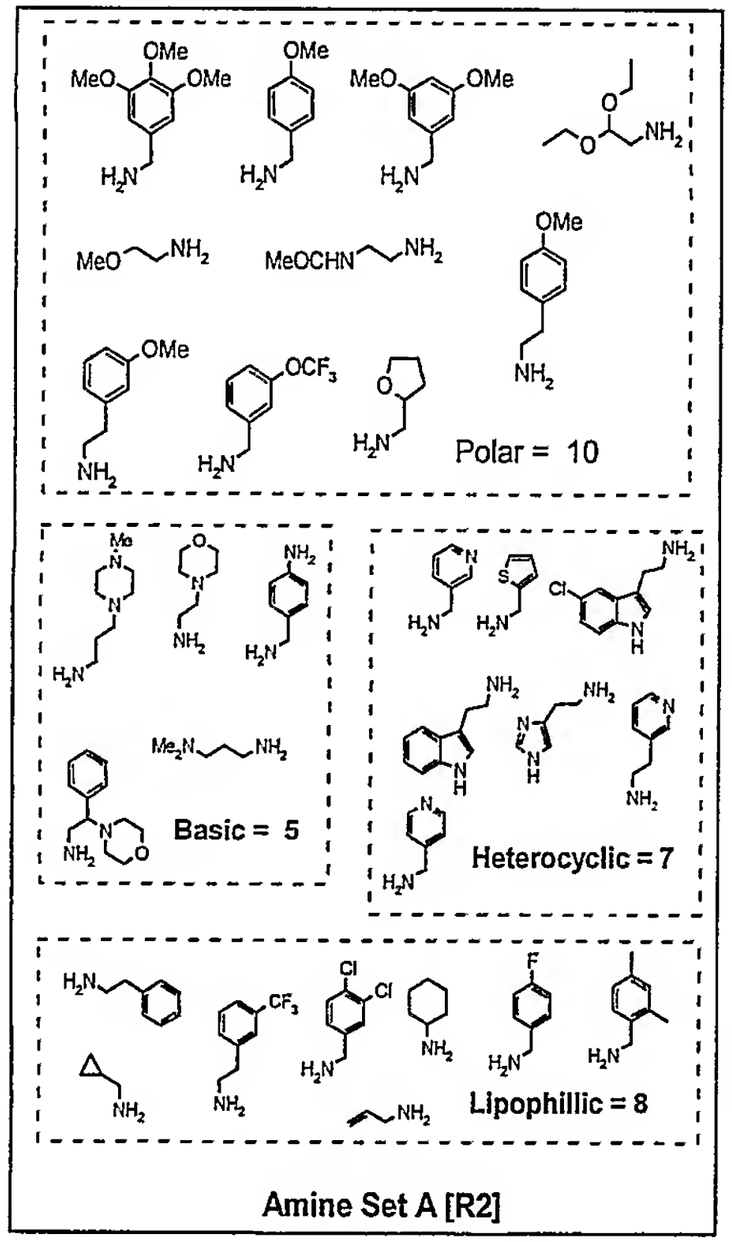
R3 is aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which

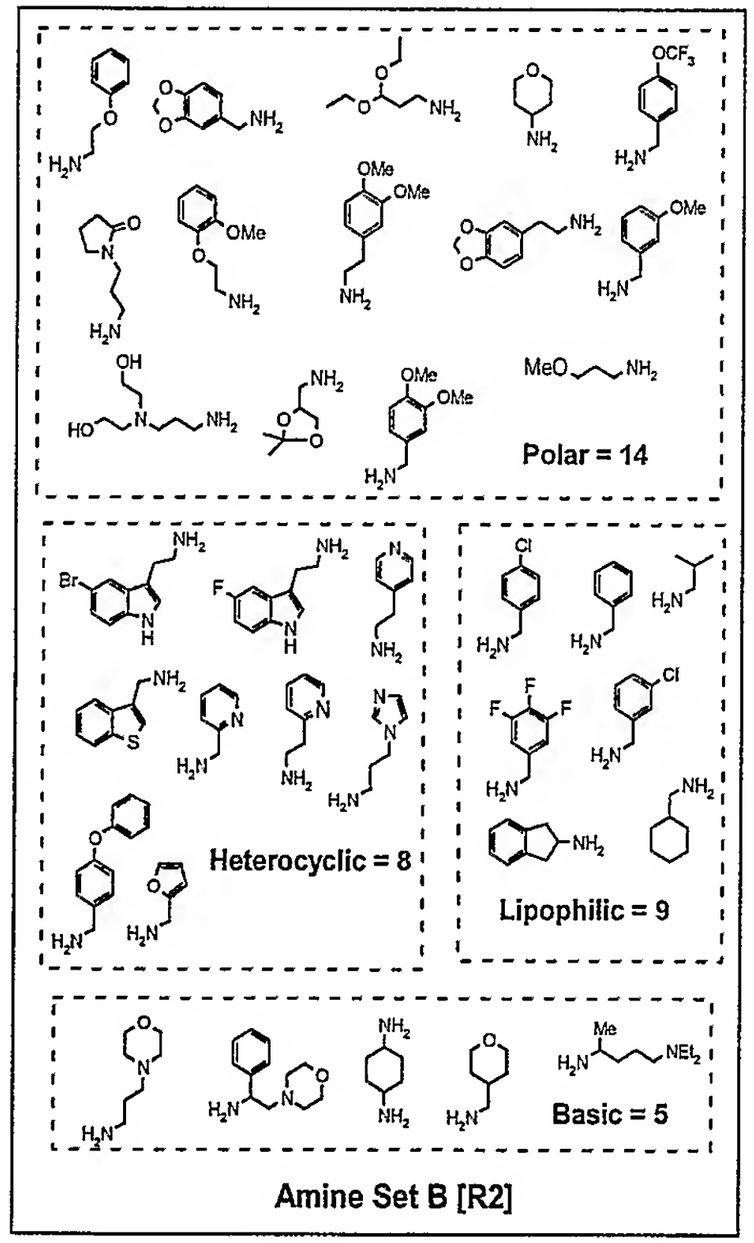
may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

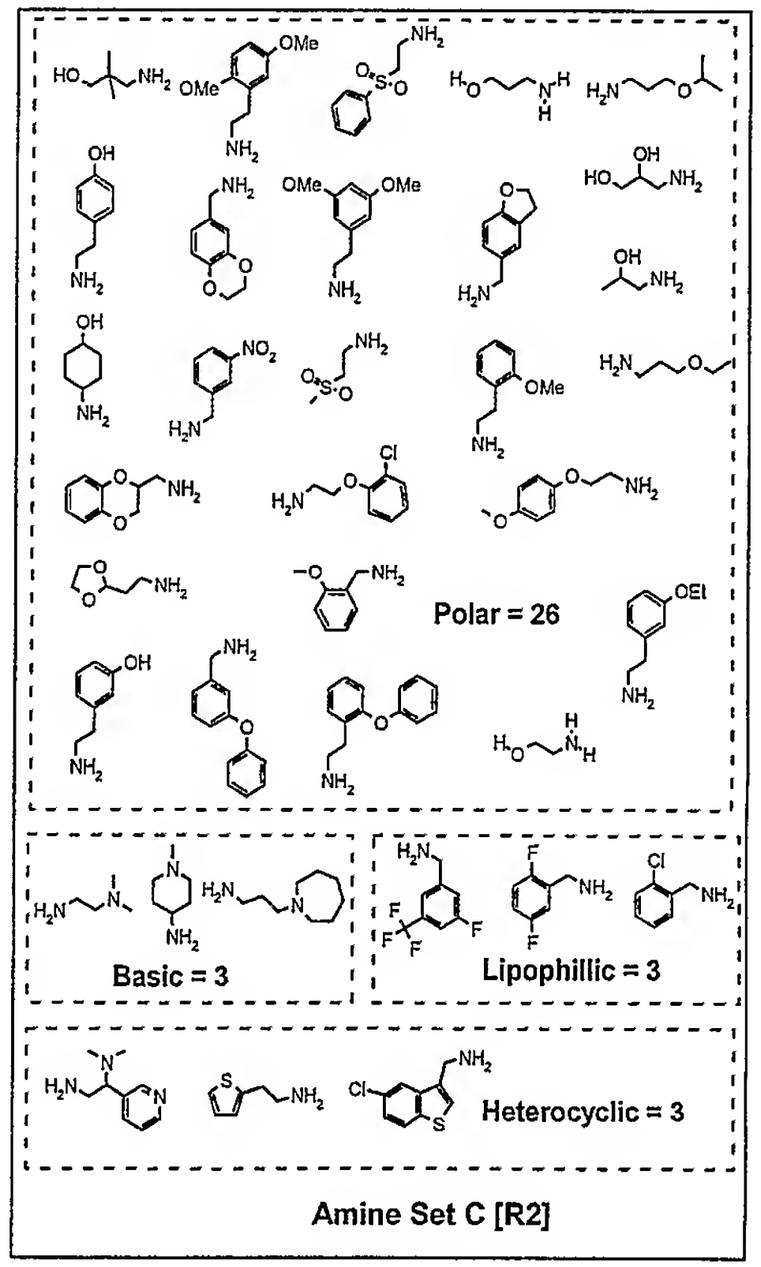
6. A library according to claim 5 which comprises or consists of a structurally related set of compounds, said library comprising compounds selected from the compounds shown by the following scatter diagrams:

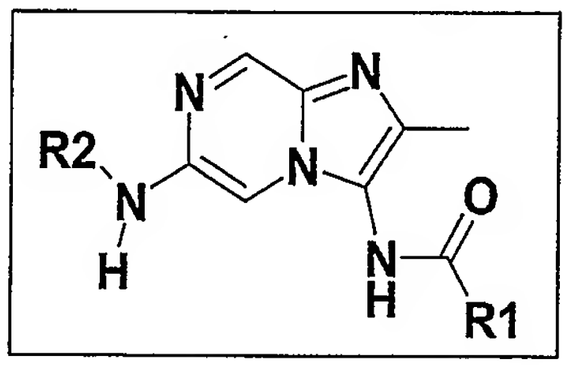


SFK10 Formula I

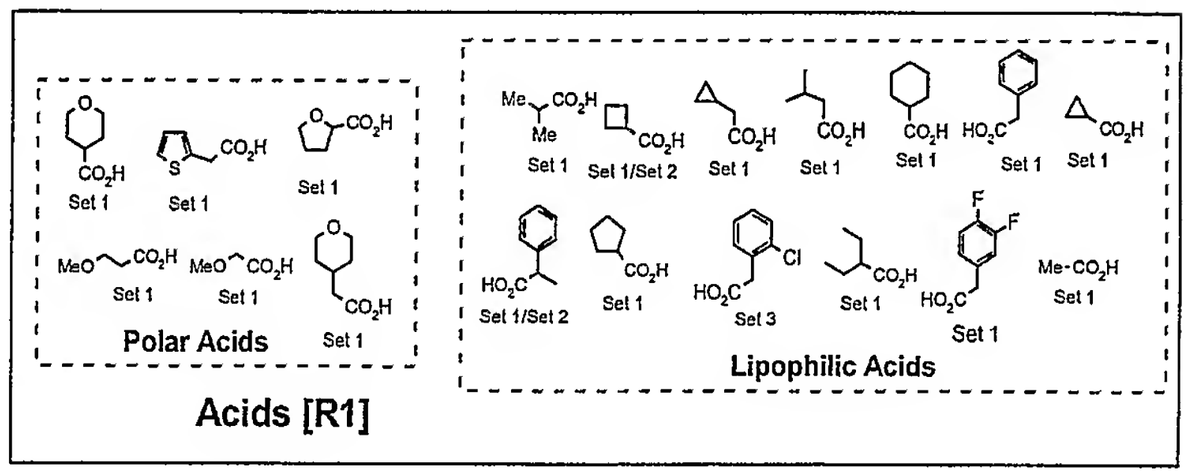


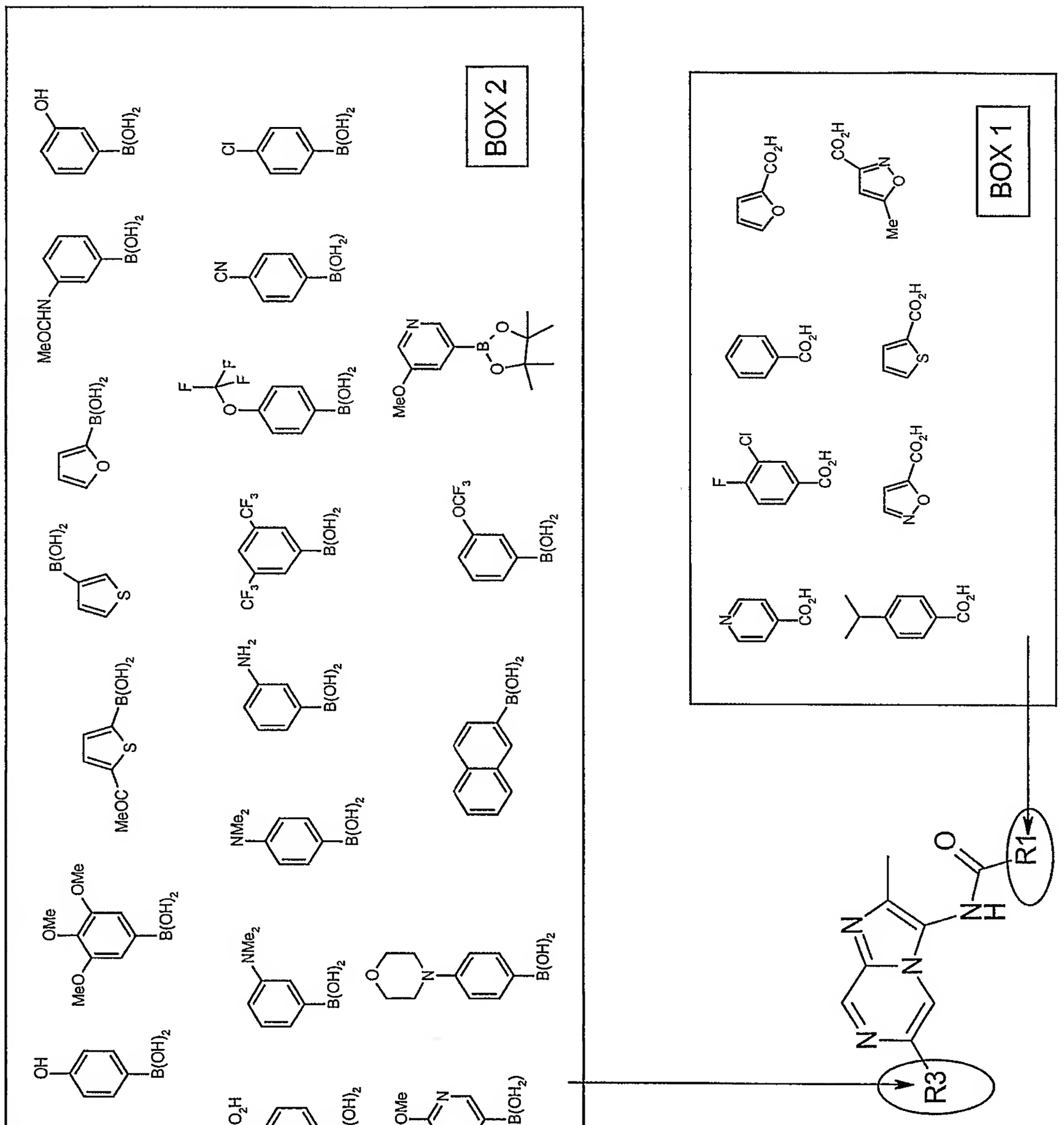




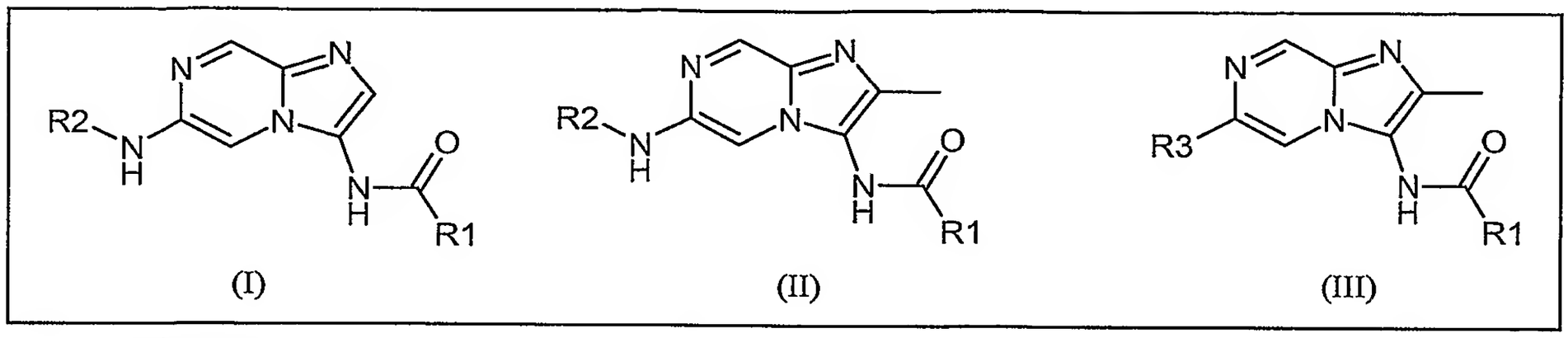


SFK10 Formula II




BOX 1
BOX 2
SFK10 Formula (III)
R1
R3

7. A compound having a core chemical structure (scaffold) which is selected from Formula I and/or formula II and/or formula III:



wherein

R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

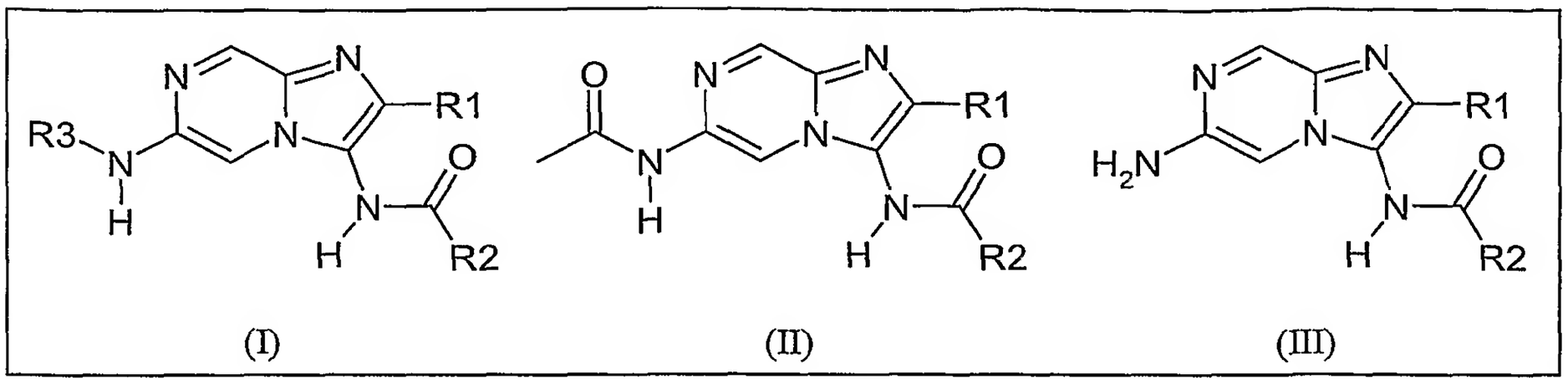
R2 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure

containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

R3 is aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

8. A compound according to claim 7 which is selected from the compounds represented within the library of claim 6.

9. A library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II and/or formula III:



(I) (II) (III)

wherein

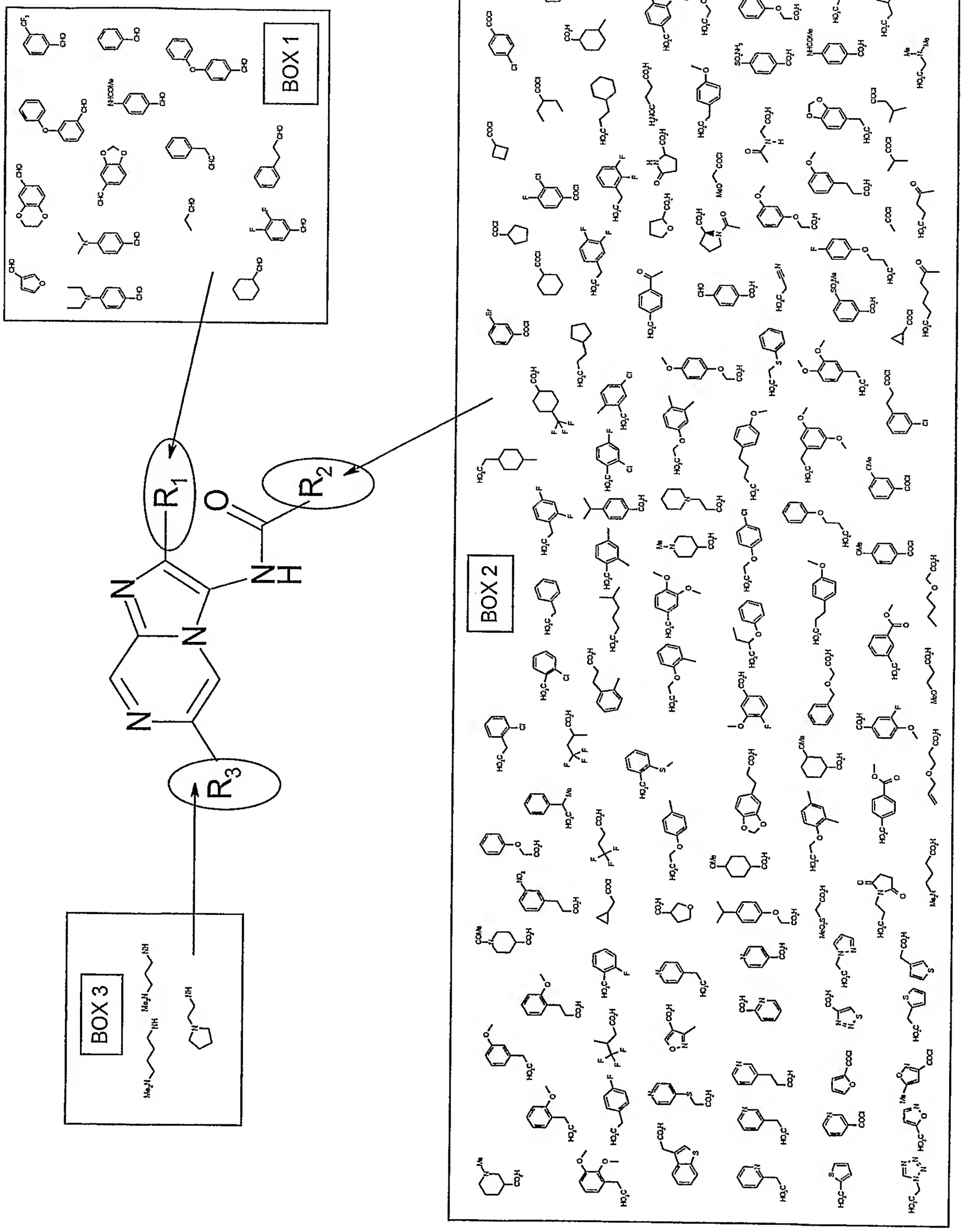
R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

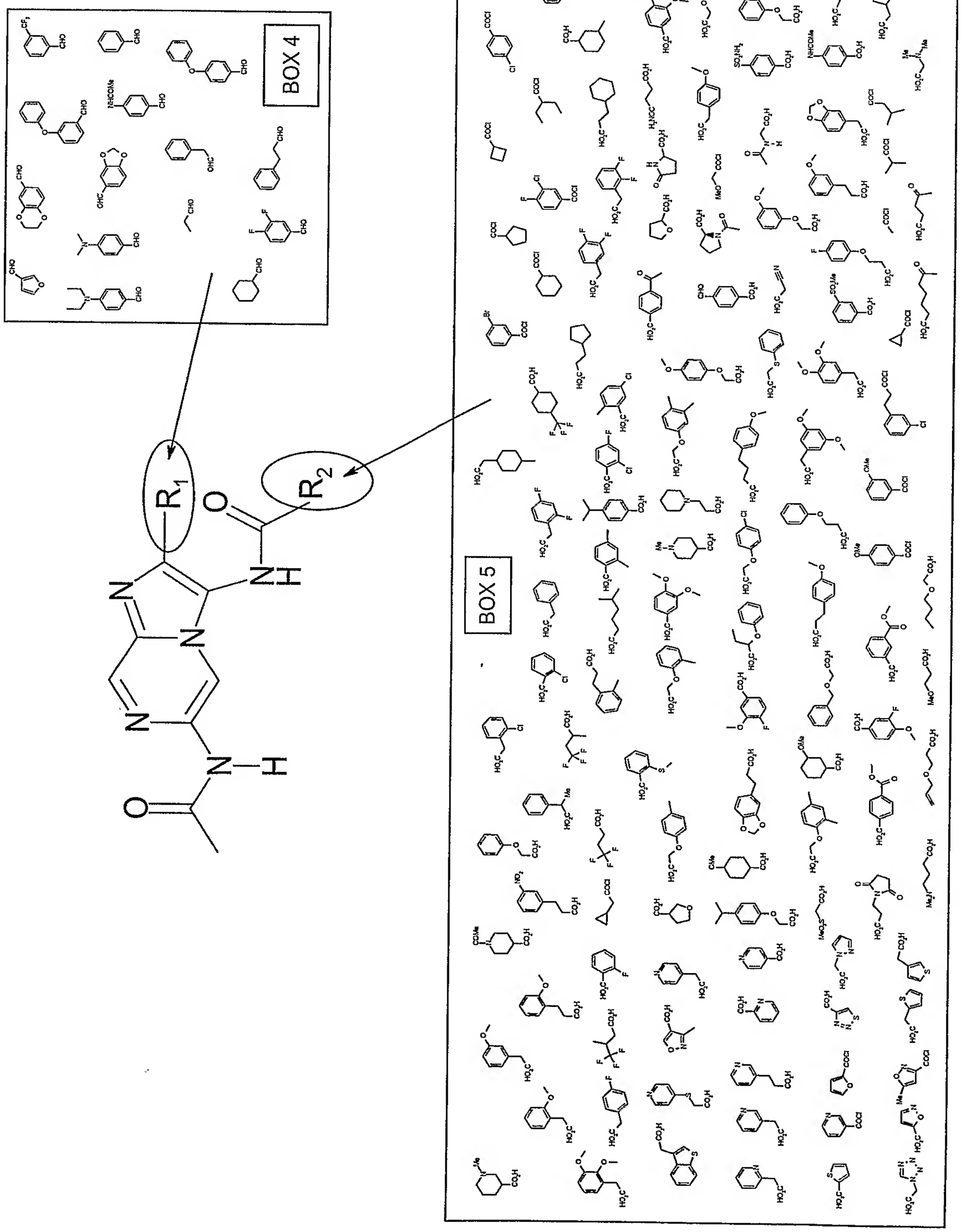
R2 is alkyl having from 1 to 20 carbon atoms which may be linear or branched and may contain one or more heteroatoms, alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or

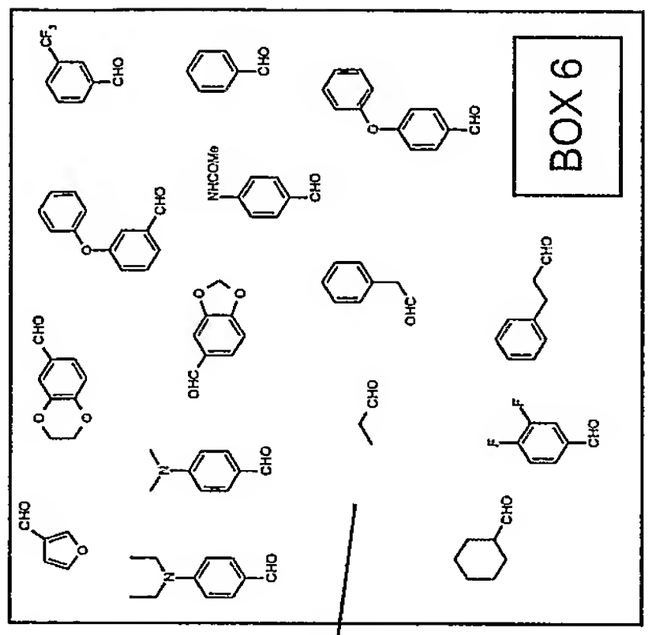
more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

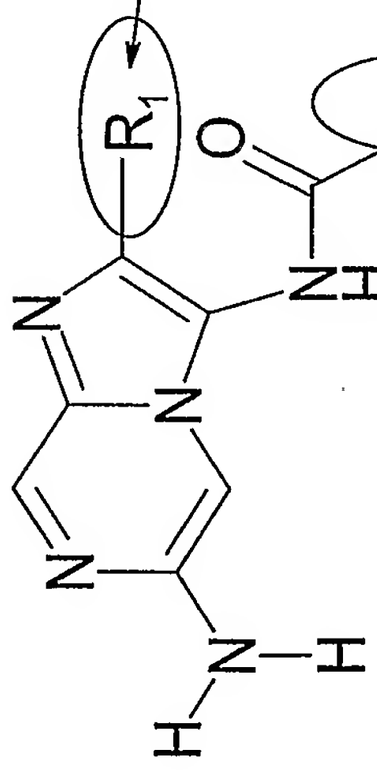
R3 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms or cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

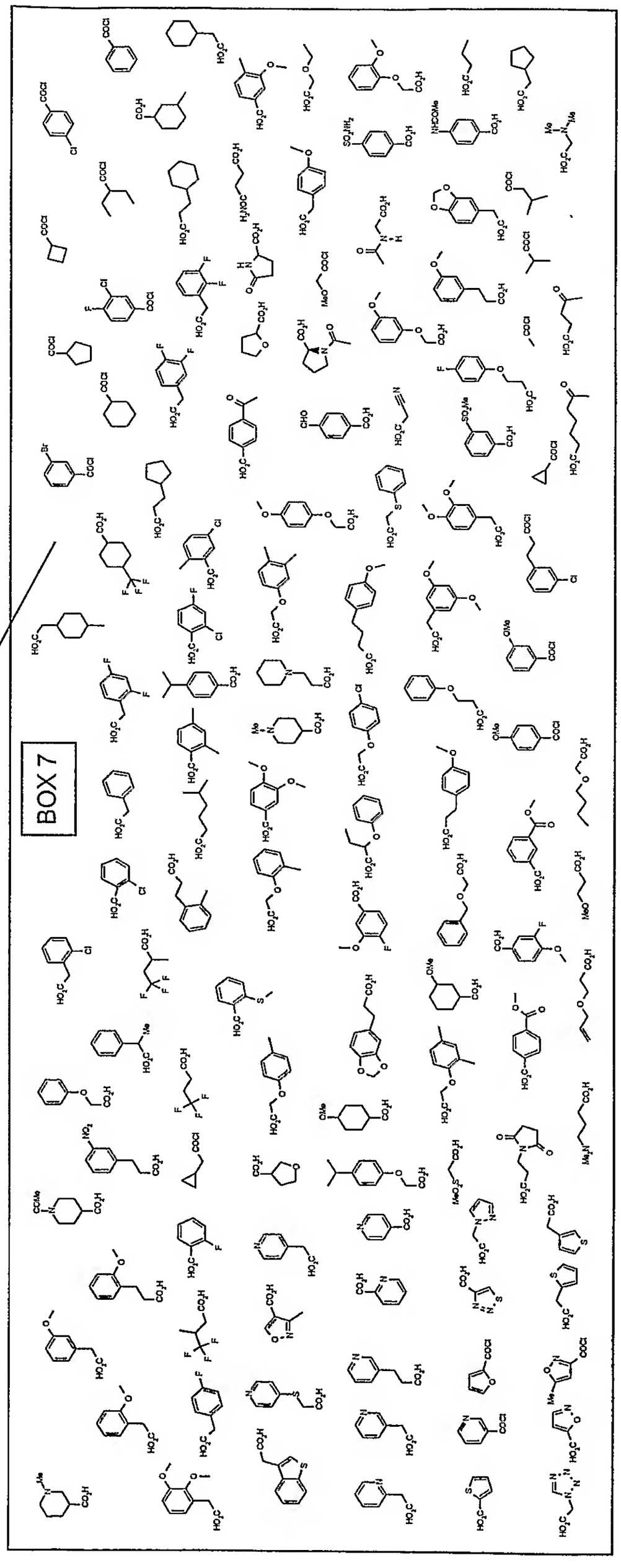
10. A library according to claim 9 which comprises or consists of a structurally related set of compounds, said library comprising compounds selected from the compounds shown by the following scatter diagrams:


BOX 1
BOX 2
BOX 3
R1
R2
R3
O
N
H
N
N
N

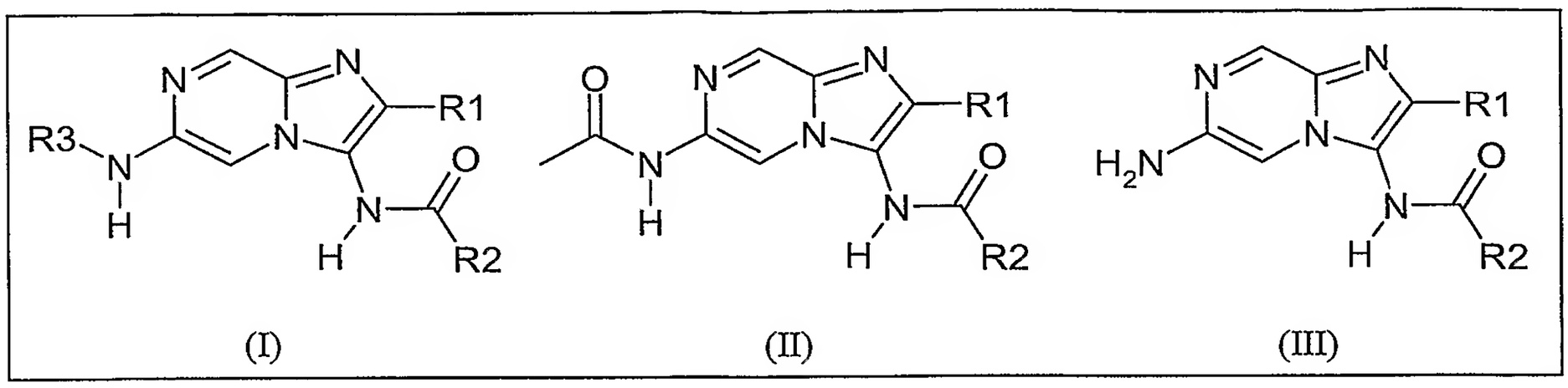

BOX 4
BOX 5
R1
R2
O
NH
N
N
N
N—H
O


BOX 6


R1
O
R2
NH
N
N
N
N
H
H


BOX 7

11. A compound having a core chemical structure (scaffold) which is selected from Formula I and/or formula II and/or formula III:



wherein

R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

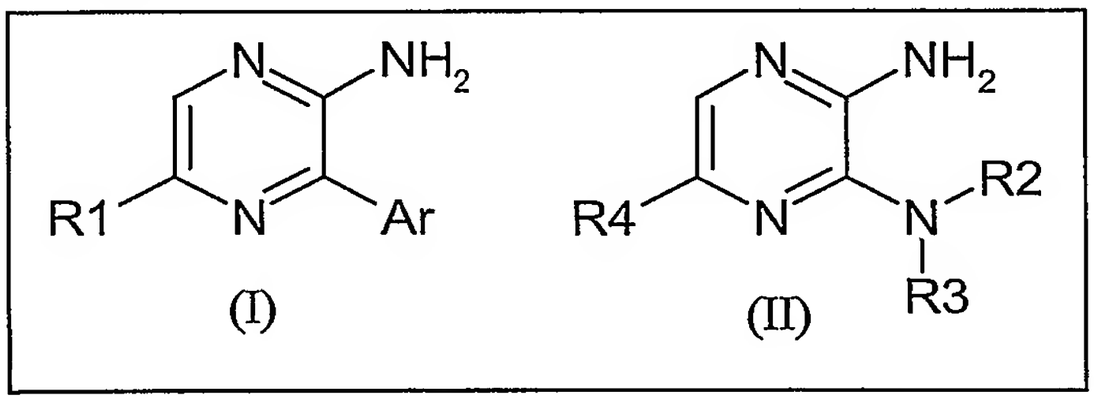
R2 is alkyl having from 1 to 20 carbon atoms which may be linear or branched and may contain one or more heteroatoms, alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more

substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

R3 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms or cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

12. A compound according to claim 11 which is selected from the compounds represented within the library of claim 10.

13. A library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I and/or formula II:



wherein

Ar is aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and contains one or more heteroatoms;

R1 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

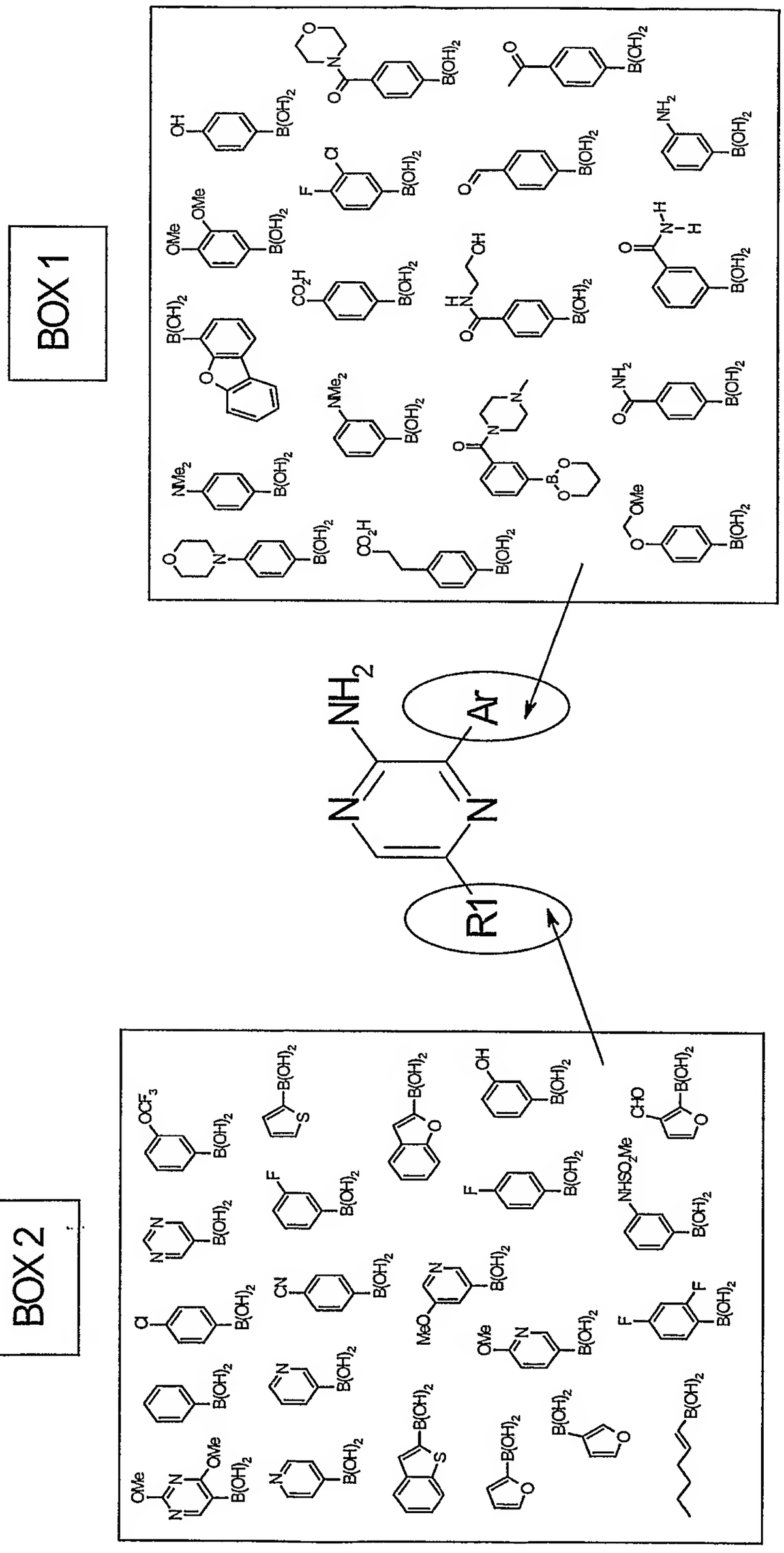
R2 is hydrogen or is joined with R3 to form the same ring system;

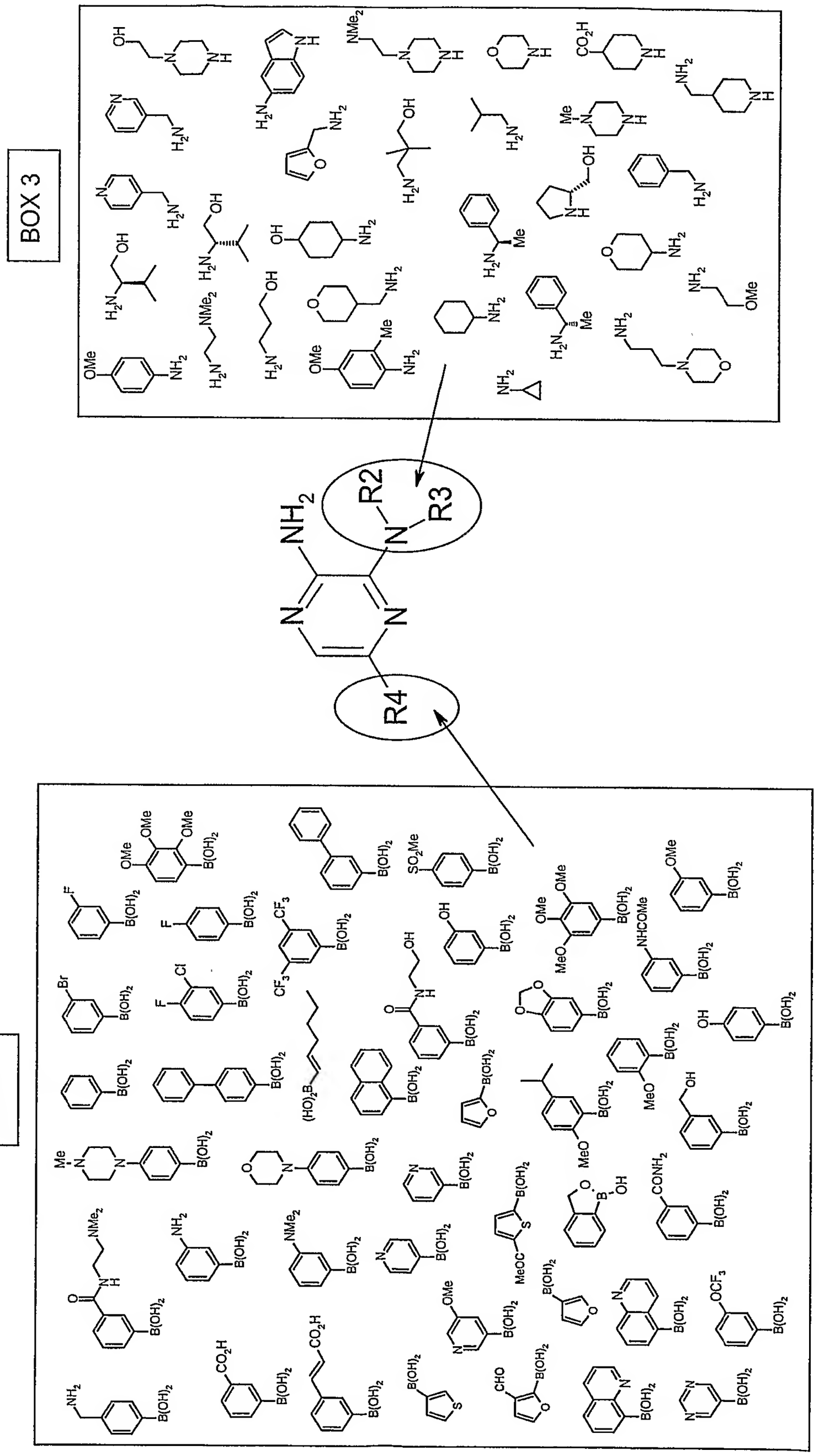
R3 is alkyl having from 1 to 20 carbon atoms which may be linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position

and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

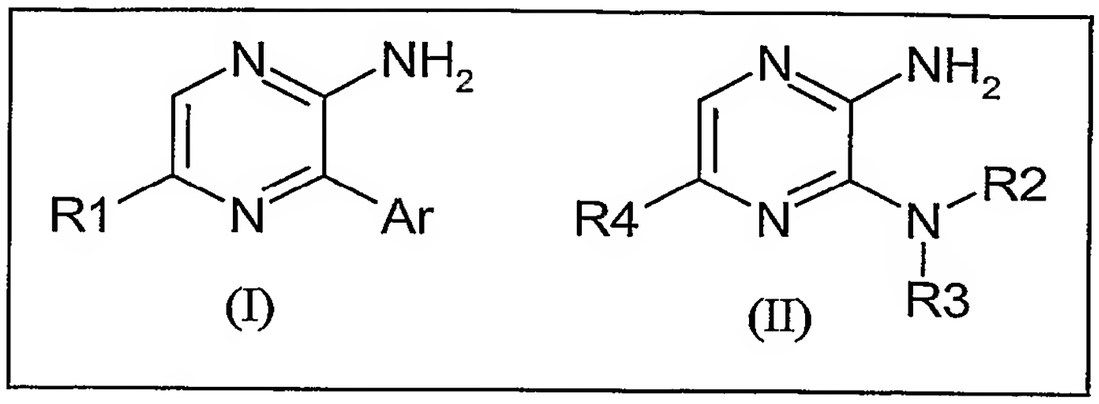
R4 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

14. A library according to claim 13 which comprises or consists of a structurally related set of compounds, said library comprising compounds selected from the compounds shown by the following scatter diagrams:


BOX 1
BOX 2
NH2
Ar
N
N
R1


BOX 3
BOX 4
NH2
R2
R3
N
N
N
N
R4

15. A compound having a core chemical structure (scaffold) of Formula I and/or formula II:



wherein

Ar is aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and contains one or more heteroatoms;

R1 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position or hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms;

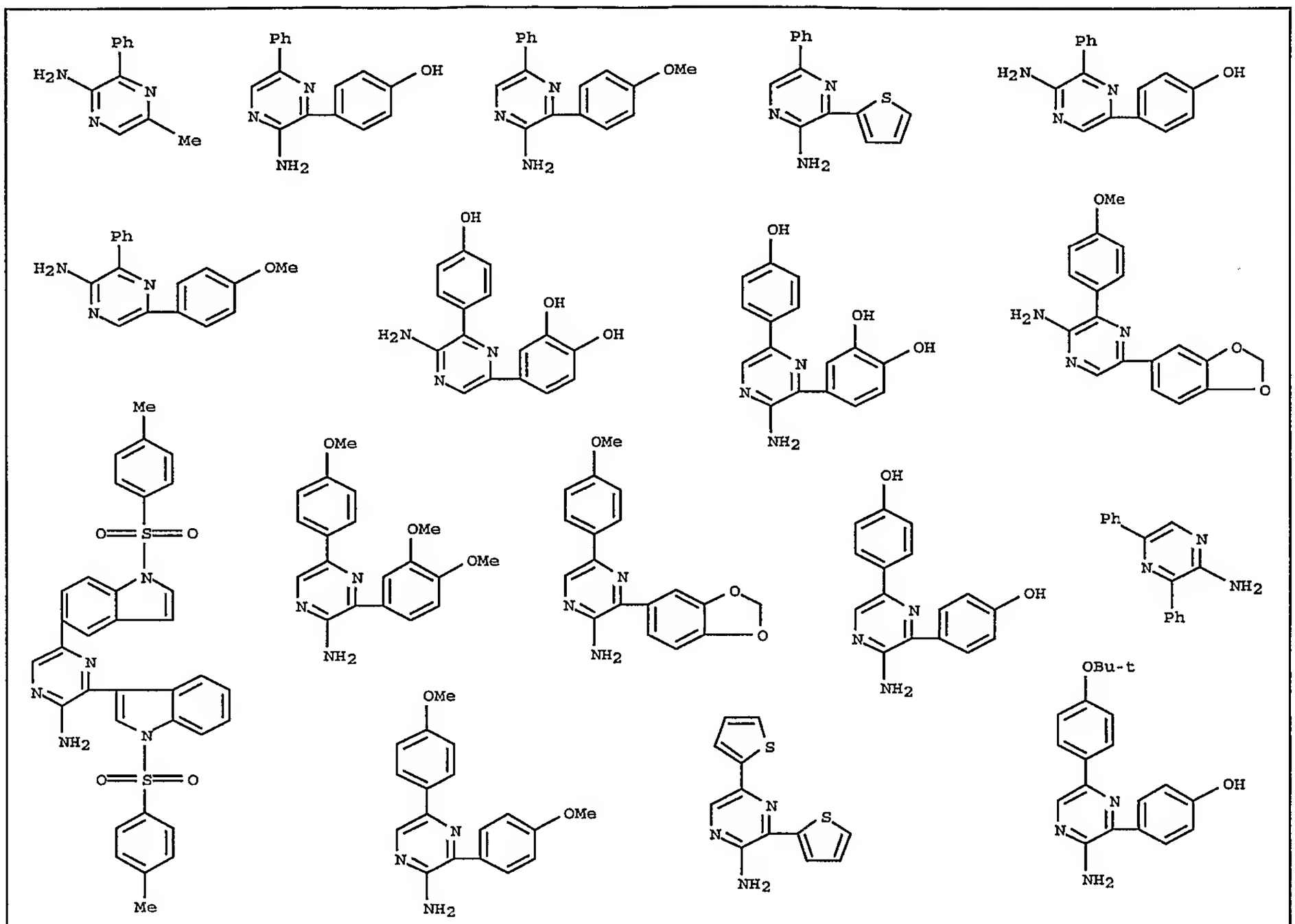
R2 is hydrogen or is joined with R3 to form the same ring system;

R3 is alkyl having from 1 to 20 carbon atoms which may be linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more

substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

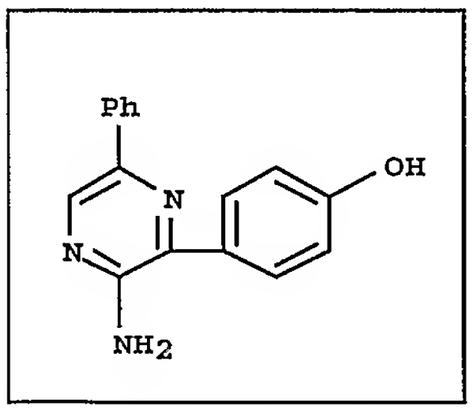
R4 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

excluding:



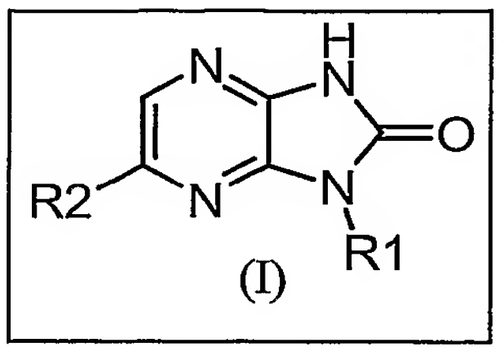
Mentioned in literature

and



16. A compound according to claim 15 which is selected from the compounds represented within the library of claim 14.

17. A library comprising or consisting of a set of structurally related compounds having a core chemical structure (scaffold) of Formula I:



(I)

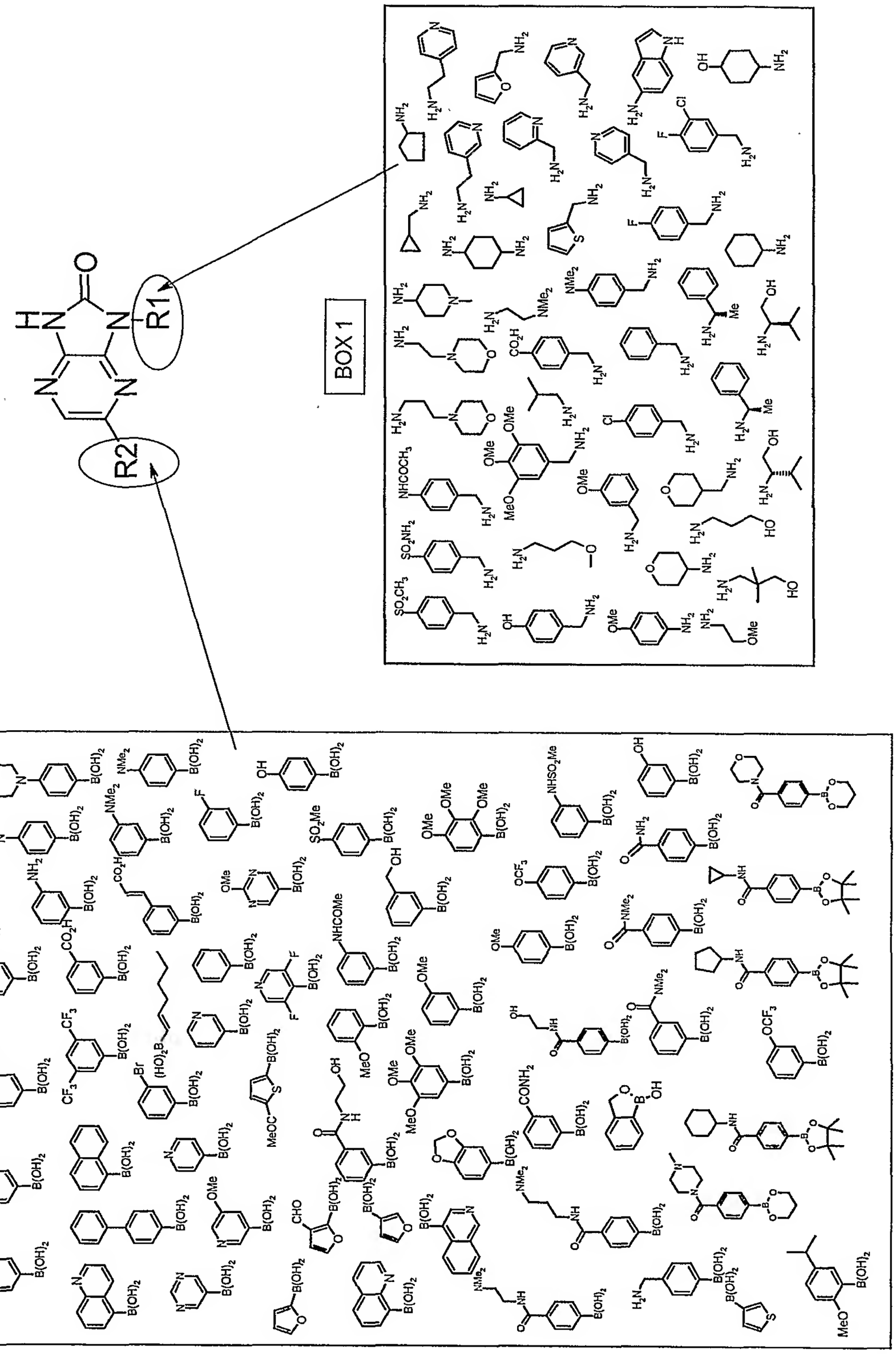
wherein

R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

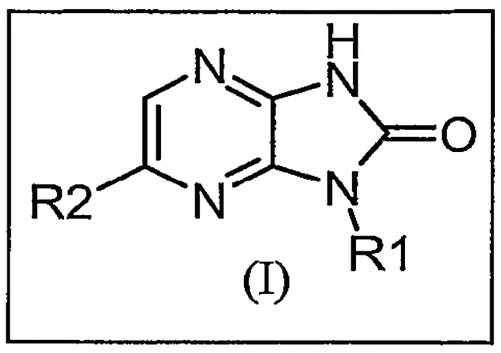
R2 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having

from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

18. A library according to claim 17 which comprises or consists of a structurally related set of compounds, said library comprising compounds selected from the compounds shown by the following scatter diagram:


BOX 1
R1
R2
BOX 2

19. A compound having a core chemical structure (scaffold) which is:



(I)

wherein

R1 is alkyl having from 1 to 20 carbon atoms which may linear or branched and may contain one or more heteroatoms, cycloalkyl having from 3 to 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms; and

R2 is alkenyl having from 1 to 20 carbon atoms, aryl having a cyclic aromatic structure containing between 2 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, aryl having a cyclic aromatic structure containing between 3 and 20 carbon atoms which may bear one or more substituent groups at any available ring position, hetero aryl having a cyclic aromatic structure containing between 1 and 20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms, aralkyl having

from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms or heteroaralkyl having from 1-20 carbon atoms which may bear one or more substituent groups at any available ring position and may contain one or more heteroatoms.

20. A compound according to claim 19 which is selected from the compounds represented within the library of claim 18.

21. A library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17 or 18 which comprises compounds having a core chemical structure and permitted substituents thereon, and said library has all or substantially all of the permitted substitutions represented by compounds therein.

22. A library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18 or 21 which comprises compounds having a core chemical structure and permitted substituents thereon, and said library has at least about 100, at least about 1000, at least about 2000, at least about 3000 or at least about 10000 compounds represented therein.

23. A method for making a compound library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22 which method includes the steps of any of the schemes described herein for making a core chemical structure (scaffold) of a library.

24. A method of making a compound according to any one of claims 3, 4, 7, 8, 11, 12, 15, 16, 19 or 20, which method includes the steps of any of the schemes described herein for making compounds of a library.

25. An assay comprising a library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22, or one or more compounds according to any of claims 3, 4, 7, 8, 11, 12, 15, 16, 19 or 20.

26. Use of an assay according to claim 25 for identifying a compound which has therapeutic affect or importation of a compound identified using an assay according to claim 25.

27. A pharmaceutical composition which comprises a compound having a core chemical structure (scaffold) of a library selected from a library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22;
or a compound according to any one of claims 3, 4, 7, 8, 11, 12, 15, 16, 19 or 20;
or a compound identified in an assay according to claim 25.

28. A compound having a core chemical structure (scaffold) of a library selected from a library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22;
or a compound according to any one of claims 3, 4, 7, 8, 11, 12, 15, 16, 19 or 20 for use in therapy.

29. Use of a compound having a core chemical structure (scaffold) of a library selected from a library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22;
or a compound according to any one of claims 3, 4, 7, 8, 11, 12, 15, 16, 19 or 20 in the manufacture of a medicament for treatment or prophylaxis of a condition characterised by abnormal kinase activity.

30. Use of a compound having a core chemical structure (scaffold) of a library selected from a library according to any one of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22;

or a compound according to any one of claims 3, 4, 7, 8, 11, 12, 15, 16, 19 or 20 in the manufacture of a medicament for treatment or prophylaxis of a condition selected from cancer, a tumour, metastases, inflammation or diabetes.

31. A family of libraries of compounds for high throughput investigation of a predetermined kinase enzyme wherein the family includes at least two of the libraries according to any of claims 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21 or 22.

32. A method for making a family of libraries according to claim 31, which method comprises the steps of the schemes described herein.